Novel 1-Amino Triazolo [4,3-a] Quinazoline-5-ones and/or –5-thiones inhibitors of Phosphodiesterases IV

Field of the invention

The present invention relates to novel triazolo [4,3-a] quinazoline-5-ones and/or –5-thiones useful for drug preparation for treatment by therapy with a phosphodiesterases 4 inhibitor. These drugs are useful in particular as anti-inflammatories, anti-allergics, bronchodilatators, anti-asthmatics, or TNFα. inhibitors.

Background of the invention

The cyclic adenosine 3', 5'-monophosphate (AMPc) is an second ubiquitous intracellular messenger, acting as an intermediate between a first messenger (hormone, neurotransmitter, or autacoid) and the cellular functional responses: the first messenger stimulates enzyme responsible of the AMPc synthesis; AMPc intervenes then, relying of the cells implicated, in very numerous functions: metabolic, contractile, or secretory.

The effects of AMPc terminate when it is broken down by cyclic nucleotide phosphodiesterases, intracellular enzymes that catalyze its hydrolysis into inactive adenosine 5'-monophosphate.

In mammals we distinguish at least seven large families of cyclic nucleotide phosphodiesterases (PDE) numbered from 1 to 7 according to their structure, their kinetic behavior, their substrate specificity, or their sensitivity towards effectors (Beavo J.A. et al (1990) Trends Pharmacol. Sci. 11, 150-155. Beavo J.A. et al (1994) Molecular Pharmacol. 46, 399-405). PDE4s are specific to AMPc.

Some phosphodiesterase non-specific inhibitors are known as inhibiting several families of enzymes. This is the case for some methylxanthins like theophyllin. These compounds have a weak therapeutic index, in particular because of their action on some classes of PDE present in cells other than target cells. Additionally, some families of PDE may be selectively inhibited by various pharmacological agents : hydrolysis of cyclic nucleotides slowed down and therefore their concentration increase in only cells the type of PDE sensitive to the inhibitor is found.

Of interest are the phosphodiesterases 4 (PDE4), which have been identified in numerous tissues including the central nervous system, heart, vascular endothelium, vascular smooth muscle and the one of air passage muscle, myeloid and lymphoid lines.

AMPc increase in cells implicated in inflammation inhibits their activation : inhibition of synthesis and mediator release in mastocytes, monocytes, eosinophil and basophil polynuclears, inhibition of chimiotactism and degranulation of eosinophil and neutrophil polynuclears, inhibition of division and differentiation of lymphocytes.

The cytokins, in particular TNF and interleukins, produced by different leukocyte classes such as T lymphocytes and eosinophil polynuclears, play an important role in the triggering of inflammatory manifestations in particular in response to stimulation by an allergen in respiratory tracts.

Further, AMPc decreases air passage smooth muscular fiber tonicity; PDE4 inhibitors bring about bronchorelaxation.

Chronic obstructive pneumopathy (chronic obstructive pulmonary disease or COPD) is a chronic pathology, of slow evolution, characterized by obstruction of respiratory tracts (associated with inflammation of respiratory tracts and elevated neutrophil count). Pulmonary function alteration is largely irreversible (although improvement is possible after treatment by bronchodilatators).

Clinical presentation of chronic obstructive pneumopathy may fluctuate according to attack severity, going from simple non-invalidating chronic bronchitis to very invalidating conditions like chronic respiratory insufficiencies. The main clinical characteristics of patients suffering from chronic obstructive pneumopathy are chronic bronchitis and/or emphysema (associated with respiratory tract inflammation and/or elevated neutrophil count).

Over the last years, some selective inhibitors of second-generation phosphodiesterase 4 have been suggested as potentially efficient agents in treatment of chronic obstructive pneumopathy. See, among others, Doherty, *Chemical Biology* 1999, **3**:466-473 ; Mohammed and al, *Anti-inflammatory & Immunodilatory Investigational Drugs* 1999 **1**(1) :1-28 ; Schmidt and al, *Clinical and Experimental Allergy*, **29**, supplement 2, 99-109.

Ariflo that is a PDE 4 inhibitor active by oral route, has been suggested for chronic obstructive pneumopathy treatment. See, among others : Nieman and al, Am J Respir Crit Care Med 1998, **157** :A413 ; Underwood and al, Eur Respir J 1998, **12** :86s ; Compton and al, Am J Respir Crit Care Med 1999, **159** :A522. See also the oral presentation by Compton during the meeting of the "European Respiratory Society" which was held in Madrid, on 12th October 1999, as well as the one by Torphy and Underwood during the 4th worldwide congress on inflammation which was held in Paris, from 27th to 30t^{h} June 1999. Ariflo is currently under study, in some phase III clinical trials, for chronic obstructive pneumopathy treatment.

However, we should point out that Ariflo has some drawbacks. Indeed some significant adverse events, of the nausea and vomiting type, have been reported after administering of a dose of 20 mg as a single intake. See Murdoch and al, Am J Respir Crit Care Med 1998, 157 :A409. Appearance of adverse effects at such low doses will limit the call for Ariflo and prevent use of daily single dosage pharmaceutical, leading therefore to patient discomfort.

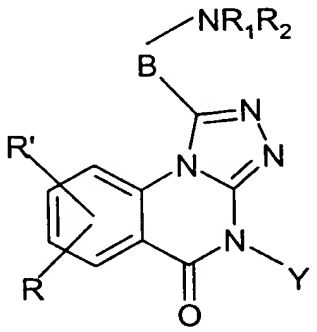
Osteoporosis is a disease characterized by bone mass decrease and skeleton architecture loss, leading to bone fracture. A large number of women, at the post-menopausal stage, suffer this disease and patient numbers keeps increasing.

Two types of distinct cells exist in bone : osteoblasts, which participate in bone formation ; and osteoclasts, which play a role in bone resorption. More particularly, bone mass results from the sum of bone formation by osteoblasts and bone resorption by osteoclasts. Consequently, molecules inhibiting bone resorption induced by osteoclasts are efficient in osteoporosis treatment. Calcitonin, biphosphonates and possibly estrogens are agents fighting against resorption and they are used in the clinical area. Molecules stimulating bone formation by osteoblasts also constitute some promising agents in osteoporosis treatment. See also, Yoshihiro et al Jpn. J. Pharmacolog. 1999, 79, 477 – 483.

For several years, extensive research has been performed to obtain and develop powerful PDE4 inhibitors. This has proved to be difficult due to the fact that lots of potential PDE4 inhibitors have some activity on phosphodiesterases in other families.

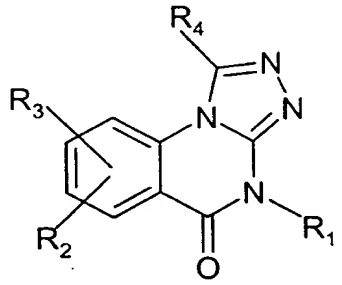
To date, the lack of selectivity of PDE4 inhibitors represents then an important problem, given the extent of functions regulated by AMPc. There is now a need for powerful and selective PDE4 inhibitors, thus without effect on PDE belonging to other families.

European patent EP 0076199 disclosed compounds with the following general formula :



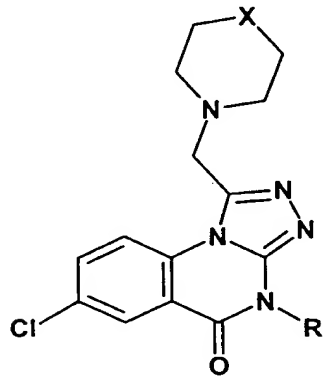
in which R and R', identical or different, represent H, halogen, alkyl C_{1-3}, alkoxy or nitro ; Y represents alkyl cycloalkyl C_{3-8}, alkenyl C_{2-4}, aryl ou aralkyl group, and B represents $(CH_2)_n$ with n = 1, 2, 3 or $CH(CH_3)$. The use of these compounds is suggested for treatment of asthma, bronchitis and allergic disorders.

Patent DDR158549 disclosed compounds with the following general formula :



in which R_1 represents H, alkyl or aryl ; R_2 and R_3 represent H, alkyl, halogen, OH, SH, O-alkyl, S-alkyl ; R_4 represents H, alkyl, halogenoalkyl, OH, SH, O-alkyl, S-alkyl, SO_2-alkyl, NH_2, SCN, aryl, $(CH_2)_nCOO$alkyl and n = 0 to 2. The use of these compounds is suggested as diuretics and antianaphylactics.

Ram and al., in J.Prakt.Chem, 1990, 332(5), 629-39 describe compounds with the following general formula :

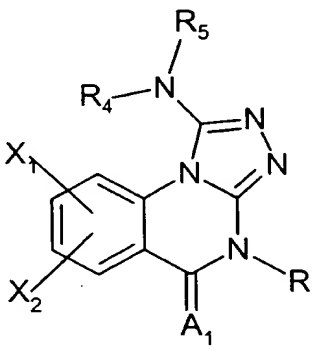


(X) R=CH_3, C_2H_5
X= C, NH, N-CH_3, N-Ar

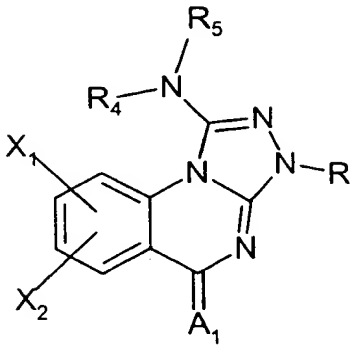
The use of these compounds is suggested for treatment of high blood pressure.

Summary f the invention

The invention related to triazolo [4,3-a] quinazoline-5-ones and/or –5-thiones of formula I or II :



I

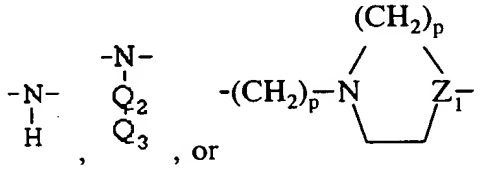


II

I and II are position isomers of group R on nitrogens 3 or 4, in which :

- A_1 is O or S ;
- X_1 and X_2, similar or different, represent :
- hydrogen, hydroxy, halogen, amino, nitro, mercapto, cyano, carboxy,
- lower alkyl, lower alkoxy or $-S(O)_mR_8$ in which m is 0, 1 or 2 and R_8 is a lower alkyl, possibly substituted by one or several halogen atoms,
- $-CO-Q_1-Q_2-Q_3$ in which :

$-Q_1-$ is : a simple valence bond, -O-,



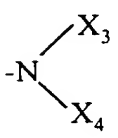
, where p is an integer between 0 to 3, and Z_1 is CH, N, O or S,

$-Q_2-$ is :

a) $-(CH_2)_q-$, q being equal to 0, 1, 2, 3, or 4, or

b) $-(CH_2-CH_2-O)_r-$, r being equal to 2, 3, or 4, and

$-Q_3$ is : -H, -OH, lower alkoxy, -O-CO- X_3 $-NHX_3$ or

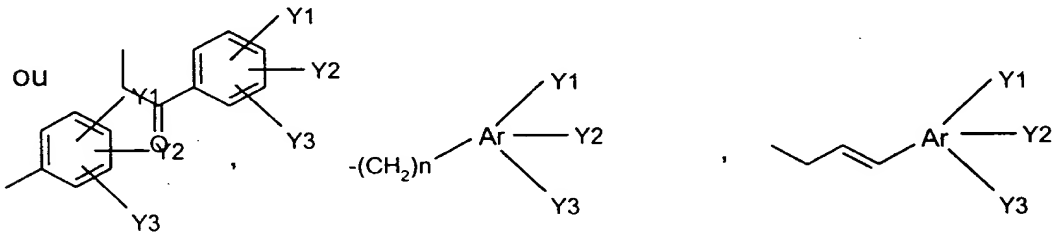


in which X_3 and X_4, similar or different, represent one group

lower alkyl, X_3 and X_4 could be bound to form a cycle, including one or several heteroatoms chosen amongst O, S or N,

- -NH-R_1 in which R_1 represents a lower alkyl group, possibly substituted by one or several groups chosen amongst halogen, hydroxy, cyano, lower alkoxy or -CO-Q_1-Q_2-Q_3, or
- -NR_2R_3 in which R_2 and R_3, similar or different, represent a lower alkyl, possibly substituted by one or several hydroxy, halogen, cyano, lower alkoxy or -CO-Q_1-Q_2-Q_3 groups, R_2 and R_3 being able to be linked to form a cycle, including one or several heteroatoms chosen amongst O, S or N and possibly bridged by a lower alkyl, gem dialkylated or substituted by one or several groups chosen amongst hydroxy, keto, lower alkyl, alkoxy or -CO-Q_1-Q_2-Q_3 ;

- R represents :
  - lower alkyl, lower alcenyl, lower alkynyl, aryl alkynyl, 2, 3 or 4 pyridylalkyl possibly substituted by a lower alkyl, a lower alkoxy, a



hydroxy, halogen or amino group,

in which :

- n is an integer between 1 and 5,
- Ar is an aromatic cycle including 5 or 6 atoms with 0 to 3 heteroatoms chosen among O, S or N.
- Y1, Y2 and Y3, similar or different represent :
  - hydrogen, hydroxy, mercapto, amino, nitro, halogen,-NHR_1, -NHR_2R_3, -$(CH_2)_s$-CN, -$(CH_2)_s$-CO-Q_1-Q_2-Q_3 in which s is an integer between 0 to 6 ;
  - lower alkyl, lower alkoxy or –$S(O)_mR_8$ in which m is 0, 1 or 2 and R_8 is a lower alkyl, each one may be possibly substituted by one or several halogen atoms ; and

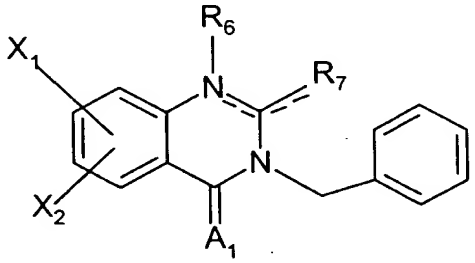
- R_4 and R_5, represent :
  - lower alkyl when R4 and R5 are similar, aralkyl, cycloalkyl or cycloalkyl alkyl, when R_4 and R_5 are different,
  - lower alkyl, R_4 and R_5 being able to be linked to form a saturated cycle or including one or several double-bonds including one or several heteroatoms chosen among O, S or N and possibly substituted by lower alkyl, hydroxy or lower alkoxy or bridged by a lower alkyl, gem dialkylated or substituted by one or several groups chosen from hydroxy, keto, lower alkyl, lower alkoxy, phenyl alkyl or $CO\text{-}Q_1\text{-}Q_2\text{-}Q_3$, two atoms of a cycle then formed may also be part of another cycle chosen among phenyl or heteroaryl comprising from 4 to 8 atoms with 1 to 4 heteroatoms ;

possibly their racemic forms and their isomers, as well as their pharmaceutically acceptable salts.

Compounds of the present invention are useful as inhibitors, particularly as selective inhibitors of phosphodiesterase enzyme, and more particularly the PDE4 enzyme.

The invention relates also to compounds mainly used as synthesis intermediaries of a formula I or II compounds.

A first series of intermediaries includes compounds having the following general formula III : in which :

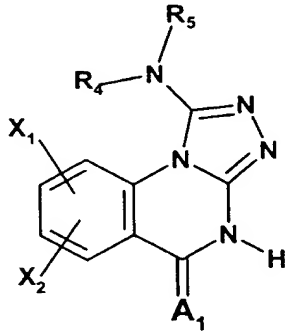


III

- X_1, X_2 and A_1 are such as defined previously ;
- the dotted lines represent optional double-bonds ;
- R_6 is hydrogen ; and
- R_7 is S or hydrazino ;

R_7 being able to be linked to nitrogen on R_6 to form a cycle, particularly a triazole, possibly substituted by a lower thioalkyl, mercapto or halogen group.

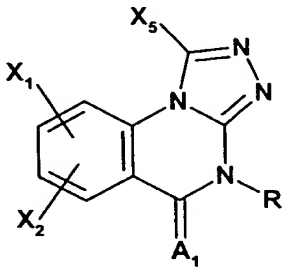
A second series of intermediaries includes compounds having the following general formula IV:



IV

in which X_1, X_2, A_1, R_4 and R_5 are such as previously defined.

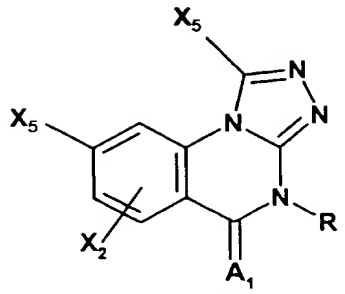
A third series of intermediaries includes compounds having the following general formula V:



(V)

in which X_1, X_2, A_1 and R are such as previously defined and X_5 is a halogen group, particularly F, Br or Cl, $-OCOX_7$, $-OSO_2X_7$ or $-SO_2X_7$ in which X_7 is a lower alkyl or an aryl group .

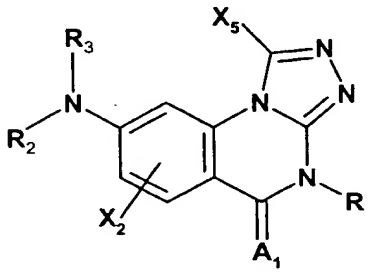
A fourth series of intermediaries include compounds having the following general formula VI :



(VI)

in which X_2, X_5, A_1 and R are such as previously defined.

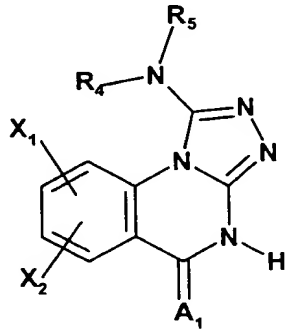
A fifth series of intermediaries include compounds having the following general formula VII :



(VII)

in which X_2, A_1, R_2 and R_3 are such as previously defined, X_5 is a halogen group, particularly F, Br or Cl, $-OCOX_7$, $-OSO_2X_7$ or $-SO_2X_7$ in which X_7 is a lower alkyl or an aryl group .

The invention relates also to a process for producing formula I and II compounds. The process is characterized as including the reaction of general formula IV compounds:



IV

in which X_1, X_2, A_1, R_4 and R_5 are such as previously defined,

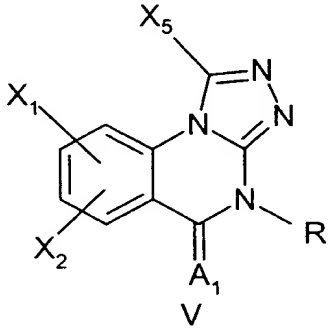
with a general formula compound

R-X'

in which R is such as previously defined and X' is a halogen group, particularly F, Br or Cl, $-OCOX_7$ or $-OSO_2X_7$ in which X_7 is a lower alkyl or aryl group ;

to obtain a mixture of general formula I and II compounds which are then possibly separated.

General formula I compounds can be also prepared by a process characterized in that it includes reacting general formula V compounds:



V

in which X_1, X_2, A_1 and R are such as previously defined and X_5 is a halogen group, particularly F, Br or Cl, $-OCOX_7$, $-OSO_2X_7$ or $-SO_2X_7$ in which X_7 is a lower alkyl or an aryl group ;

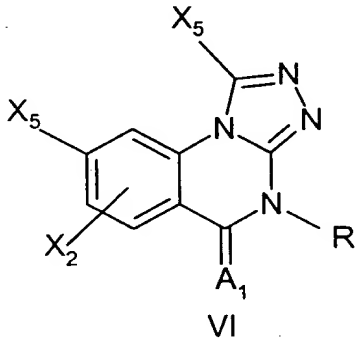
with a general formula compound :

$$HNR_4R_5$$

in which R_4 and R_5 are such as previously defined,

to obtain a general formula I compound.

In particular manner, when X_1 is $-NR_2R_3$ and $-NR_2R_3$ and $-NR_4R_5$ are identical, general formula I compounds adhering to this definition can be obtained by reacting with a general formula VI compound :



VI

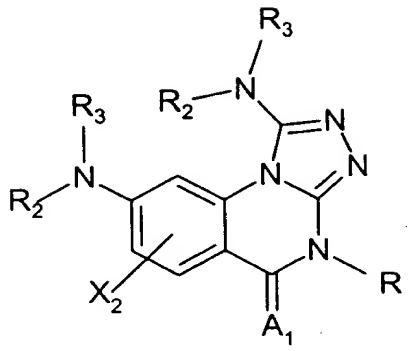
in which X_2, X_5, A_1 and R are such as previously defined,

with a general formula compound :

$$HNR_2R_3$$

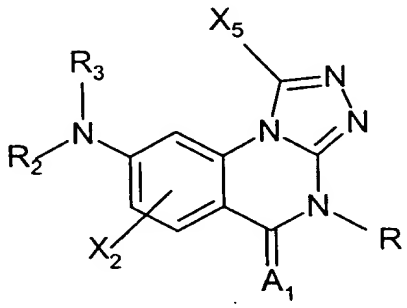
in which R_2 and R_3 are such as previously defined,

to obtain a general formula I compound :



I

Also in particular manner, when X_1 is $-NR_2R_3$ and $-NR_2R_3$ and $-NR_4R_5$ are different, general formula I compounds adhering to this definition can be obtained by reacting with a general formula VII compound :



VII

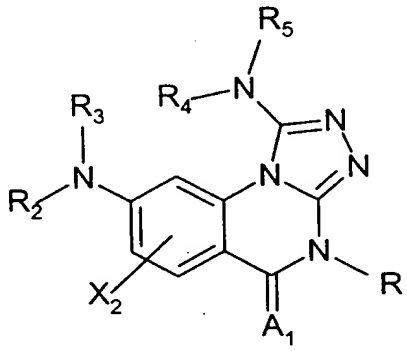
in which X_2, X_5, A_1, R, R_2 and R_3 are such as previously defined,

with a general formula compound :

$$HNR_4R_5$$

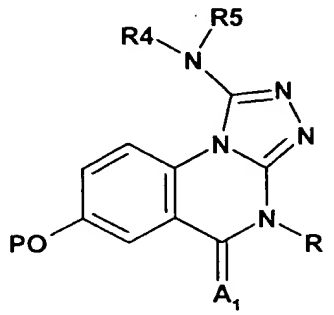
in which R_4 and R_5 are such as previously defined,

to obtain a general formula I compound :



I

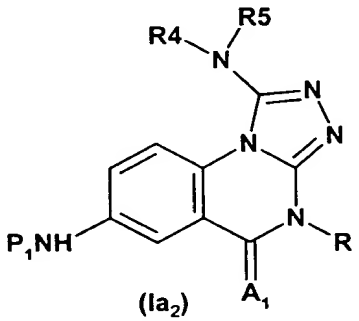
Also in particular manner, when X_1 is H and X_2 is OH, general formula I compounds adhering to this definition can be obtained by subjecting a general formula Ia_1 compound :
in which A_1, R, R_4 and R_5 are such as previously defined and P is a protector group,



(Ia_1)

to conditions allowing protector group P elimination to obtain a general formula I compound.

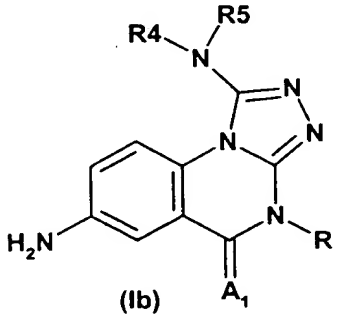
Also in particular manner, when X_1 is H and X_2 is NH_2, formula I compounds adhering to this definition can be obtained by subjecting a general formula Ia_2 compound
in which A_1, R, R_4 and R_5 are such as previously defined and P_1 is protector group,



(Ia_2)

to conditions allowing elimination of the protector group P_1 to obtain a general formula I compound.

Also in particular manner, when X_1 is H and X_2 is NHR_2 in which R2 is such as previously defined formula I compounds adhering to this definition can be obtained by reacting with a general formula Ib compound

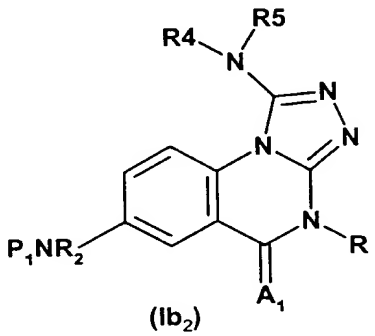


(Ib)

in which A_1, R, R_4 and R_5 are such as previously defined,

with a formula R_2X_5 compound in which R_2 and X_5 are such as previously defined, to obtain a general formula I compound.

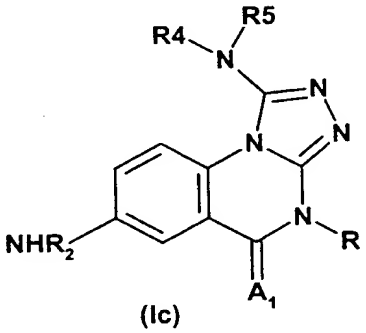
Moreover, when X_1 is H and X_2 is NHR_2 in which R_2 is such as previously defined, formula I compounds adhering to this definition can be also obtained by subjecting a general formula Ib_2 compound :



(Ib_2)

in which A_1, R, R_4 and R_5 are such as previously defined and P_1 is a protector group,
to conditions allowing protector group elimination, to obtain a general formula I compound.

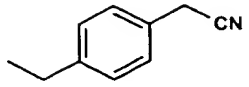
Also in particular manner, when X_1 is H and X_2 is NR_2R_x in which R_2 is such as previously defined and R_x, represents R_2 or R_3 as previously defined, formula I compounds adhering to this definition can be obtained by reacting with a general formula Ic compound :
in which A_1, R, R_2, R_4 and R_5 are such as previously described,



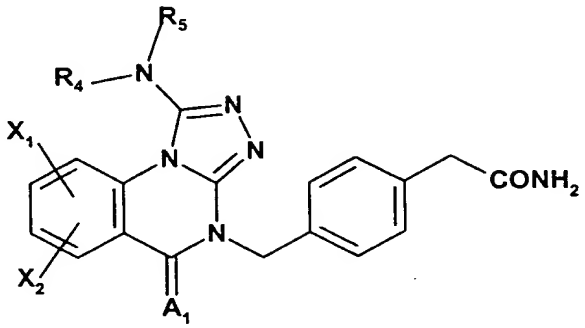
(Ic)

with a formula R_xX_5 compound in which R_x and X_5 are such as previously defined, to obtain a general formula I compound.

Also in particular manner, when R is



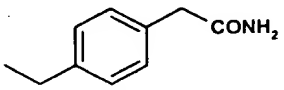
formula I compounds adhering to this definition can be obtained by dehydration of a general formula Ig compound:



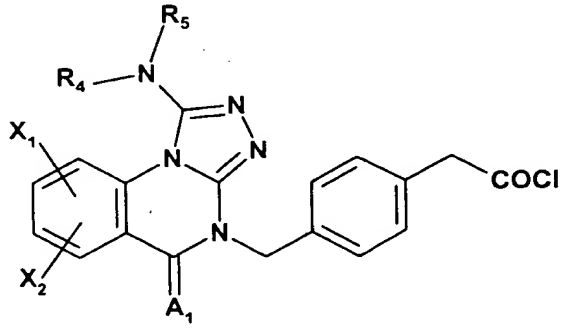
(Ig)

in which X_1, X_2, A_1, R_4 and R_5 are such as previously defined,
to obtain a general formula I compound.

Also in particular manner, when R is



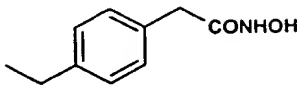
formula I compounds adhering to this definition can be obtained by reacting with a general formula If compound :



(If)

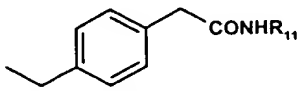
in which X_1, X_2, A_1, R_4 and R_5 are such as previously defined,
with ammonia to obtain a general formula I compound.

Also in particular manner, when R is



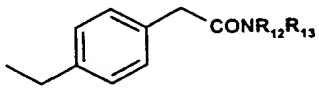
formula I compounds adhering to this definition can be obtained by reacting with a general formula If compound with hydroxylamin to obtain a general formula I compound.

Also in particular manner, when R is



formula I compounds adhering to this definition can be obtained by reacting with a general formula If compound with a formula $R_{11}NH_2$ compound in which R_{11} has the same significance than R_2, to obtain a general formula I compound.

Also in particular manner, when R is



formula I compounds adhering to this definition can be obtained by reacting with a general formula If compound with a formula $HNR_{12}R_{13}$ compound in which R_{12} and R_{13} have the same significance than R_4 and R_5 respectively, to obtain general formula I compound.

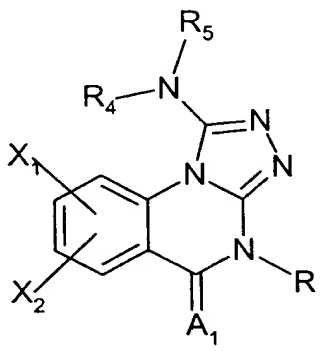
The invention relates also to a pharmaceutical composition including a formula I or II compound and a pharmacologically acceptable carrier.

The invention relates also to the use of a formula I or II compound for drug preparation in treatment disease or illness relying on therapy by phosphodiesterase inhibition, and more particularly of PDE4.

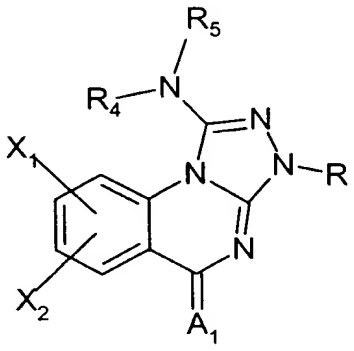
The invention relates also to a treatment method relying on therapy by phosphodiesterase inhibition, and more particularly of PDE4, said method including administering an effective concentration of a formula I or II compound to a patient.

Detailed description of the invention

The current invention relates also to general formula I or II compounds :



I



II

in which X_1, X_2, A_1, R, R_4 and R_5 are such as previously defined.

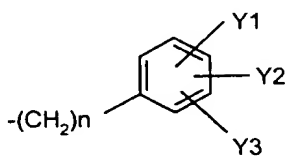
The invention relates particularly to general formula I or II compounds in which :

A_1 represents an oxygen atom ;

X_1 represents a hydrogen and X_2 is a halogen, amino, lower alkyl, hydroxy or -NHR_1 group, R1 being such as previously defined.

R represents :

- a lower alkyl, lower alcenyl, aryl alkynyl, 2-, 3- or 4-pyridylalkyl group possibly substituted on the pyridine ring by a lower alkyl, halogen or hydroxy ;



in which :

- n is an integer from 1 to 3,

- Y1, Y2 and Y3 represent each a hydrogen atom or a lower alkoxy group, more particularly methoxy,
- Y1 and Y2 represent each a hydrogen atom and Y3 represents a lower alkoxy group, amino, nitro, hydroxy group, $-(CH_2)_sCO-Q_1-Q_2-Q_3$ group, $(CH_2)_s-CN$ group in which, Q_1, Q_2, Q_3 are such as previously defined, or a lower alkyl possibly substituted by one or several halogen atoms, the particularly preferred of the substituent Y3 being the position 4, or,
- Y1 represents a hydrogen atom and Y2 and Y3, similar or different, represent a hydroxy, halogen or lower alkoxy group, or

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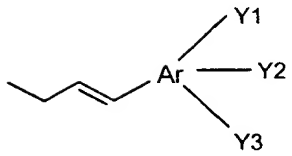


in which :

- Ar is such as previously defined ;
- Y1, Y2 and Y3 represent each a hydrogen atom, or
- Y1 and Y2 represent each a hydrogen atom and Y3 is lower alkoxy or halogen ;

R_4 and R_5, represent :

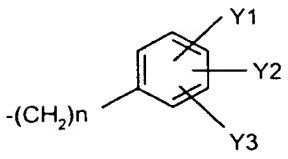
- lower alkyl when R4 and R5 are similar, aralkyl, cycloalkyl or cycloalkyl alkyl, when R_4 and R_5 are different,
- lower alkyl, R_4 and R_5 being able to be linked to form a saturated cycle or including one or several double-bonds with one or several heteroatoms chosen among O, S or N and possibly substituted by a lower alkyl, a hydroxy or a lower alkoxy or bridged by a lower alkyl, dialkylated gem or substituted by one or several groups chosen among hydroxy, keto, lower alkyl, lower alkoxy, phenyl alkyl or $CO-Q_1-Q_2-Q_3$, two atoms of the cycle then formed may also be part of another cycle chosen among phenyl or heteroaryl comprising from 4 to 8 atoms including 1 to 4 heteroatoms ;

The invention relates more particularly to general formula I compounds in which :

X_1 represents a hydrogen atom,

X_2 represents a halogen atom, amino, lower alkyl, hydroxy or --NHR_1 ;

R represents :



in which :

- n is an integer from 1 to 3,
- Y1, Y2 and Y3 represent each a hydrogen atom or a lower alkoxy group, more particularly methoxy and in particular 3, 4, 5-trimethoxy,
- Y1 and Y2 represent each a hydrogen atom and Y3 represents a lower alkoxy group, amino, nitro, or hydroxy, a lower alkyl group possibly substituted by one or several halogen atoms, a $-(CH_2)_sCO-Q_1-Q_2-Q_3$ group in which s is 0 or 1, Q_1 is O, -NH- or a valence bond, Q_2 is $-(CH_2)_q-$, q being equal to 0, 1, 2, 3 or 4 and Q_3 is H, OH or $-NX_3X_4$ in which X_3 and X_4 are such as previously defined, a $(CH_2)_s$-CN group in which s is 0 or 1, the position particularly preferred of the substituent Y3 being the position 4, or
- Y1 represents a hydrogen atom and Y2 and Y3, similar or different, represent a hydroxy, halogen or lower alkoxy group; or

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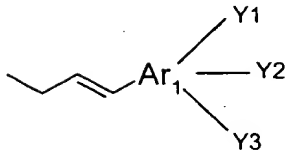


in which :

-

- Ar_1 is an aromatic cycle including 6 atoms, one may be a nitrogen atom in position 2, 3 or 4 and preferably in position 3 ;
- Y1, Y2 and Y3 represent each a hydrogen atom, or

- Y1 and Y2 represent each a hydrogen atom and Y3 is a lower alkoxy group or a halogen group when Ar_1 does not include a nitrogen atom; and

R_4 and R_5, represent :

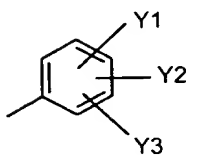
- lower alkyl when R_4 and R_5 are similar, aralkyl, cycloalkyl or cycloalkyl alkyl, when R_4 and R_5 are different,
- lower alkyl, R_4 and R_5 being able to be linked to form a saturated cycle or including one or several double-bonds with one or several heteroatoms chosen among O, S or N and possibly substituted by a lower alkyl, a hydroxy or a lower alkoxy or bridged by a lower alkyl, dialkylated gem or substituted by one or several groups chosen among hydroxy, keto, lower alkyl, lower alkoxy, phenyl alkyl or $CO\text{-}Q_1\text{-}Q_2\text{-}Q_3$, two atoms from the cycle then formed may also be part of another cycle chosen among phenyl or heteroaryl comprising from 4 to 8 atoms with 1 to 4 heteroatoms ;

The invention relates also to general formula I or II compounds in which :

X_1, X_2, A_1, R_4 and R_5 are such as previously defined in the summary of the invention ; and

R represents :

- lower alkynyl, aryl alkynyl, 2-, 3- or 4-pyridylalkyl possibly substituted by a lower alkyl, a lower alkoxy, a hydroxy or a halogen group ,



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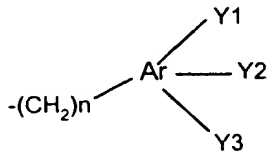

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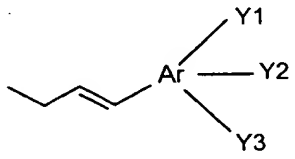

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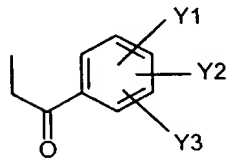

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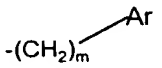

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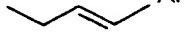


in which :

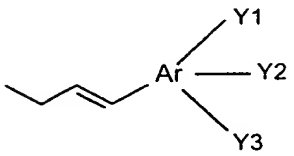
- n is an integer from 1 to 5 and m is an integer from 3 to 5 ;

- Ar is an aromatic cycle including 5 or 6 atoms with 0 to 3 heteroatoms chosen among O, S or N ;
- Y1, Y2 and Y3, similar or different represent :
  - hydroxy, mercapto, amino, nitro, halogen, $-(CH_2)_sCO-Q_1-Q_2-Q_3$, $(CH_2)_s-CN$, in which s is an integer from 0 to 6, lower alkyl, lower alkoxy or lower thioalkyl, possibly substituted by one or several halogen atoms.

In another of its embodiments, the current invention relates to general formula I or II compounds in which :

X_1, X_2, R_4 and R_5 are such as previously defined in the summary of the invention ; and

R represents :



in which :

- Ar is an aromatic cycle including 5 or 6 atoms with 0 to 3 heteroatoms chosen among O, S or N (aromatic cycles including 6 atoms, one atom could be a nitrogen in position 2, 3 or 4, preferably in position 3);
- Y1, Y2 and Y3, similar or different represent :
  - hydrogen, hydroxy, mercapto, amino, nitro, halogen, cyano, $-(CH_2)_sCO-Q_1-Q_2-Q_3$ in which s is an integer from 0 to 6, lower alkyl, lower alkoxy or lower thioalkyl, possibly substituted by one or several halogen atoms.

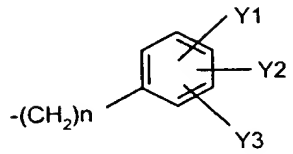
In a preferred manner :

- Y1, Y2 and Y3 represent each a hydrogen atom, or
- Y1 and Y2 represent each a hydrogen atom and Y3 is a lower alkoxy or halogen.

In another of its embodiments, the current invention relates to general formula I or II compounds in which :

X_1, X_2, A_1, R_4 and R_5 are such as previously defined above in the summary of the invention ; and

R represents :



in which :

- n is an integer from 1 to 3 ;
- Y1, Y2 and Y3, similar or different represent :
  - hydroxy, mercapto, amino, nitro, halogen, $-(CH_2)_sCO-Q_1-Q_2-Q_3$, $(CH_2)_s-CN$ in which s is an integer from 0 to 6, lower alkyl, lower alkoxy or lower thioalkyl, possibly substituted by one or several halogen atoms.

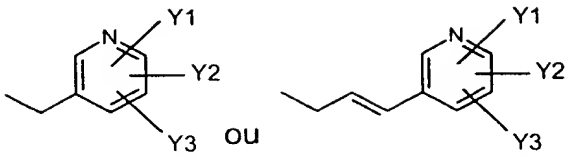
In a preferred manner :

- n is an integer from 1 to 3,
- Y1, Y2 and Y3 represent each a lower alkoxy group, more particularly methoxy and in particular 3, 4, 5-triméthoxy,
- Y1 and Y2 represent each a hydrogen atom and Y3 represents a lower alkoxy group, cyano, amino, nitro or hydroxy, a lower alkyl group possibly substituted by one or several halogen atoms or a $-(CH_2)_sCO-Q_1-Q_2-Q_3$ group in which s is 0 or 1, Q_1 is O, -NH- or a valence bond, Q_2 is $-(CH_2)_q-$, q being equal to 0, 1, 2, 3 or 4 and Q_3 is H, OH or $-NX_3X_4$ in which X_3 and X_4 are such as previously defined, the position particularly preferred of substituent Y3 being position 4, or
- Y1 represents a hydrogen atom and Y2 and Y3, similar or different, represent a hydroxy, halogen or lower alkoxy group.

In another of its embodiments, the current invention relates to general formula I or II compounds in which

X_1, X_2, A_1, R_4 and R_5 are such as previously defined in the summary of the invention; and

R represents :



in which :

- Y1, Y2 and Y3, similar or different represent :
  - hydrogen, hydroxy, mercapto, amino, nitro, halogen, $-(CH_2)_sCO-Q_1-Q_2-Q_3$, $(CH_2)_s-CN$, in which s is an integer from 0 to 6, lower alkyl, lower alkoxy or lower thioalkyl, possibly substituted by one or several halogen atoms.

In a preferred manner :

- Y1, Y2 and Y3 represent each a hydrogen atom, or
- Y1 and Y2 represent each a hydrogen atom and Y3 is lower alkoxy or halogen.

In another of its embodiments, the current invention relates to general formula I or II compounds in which

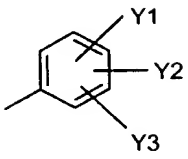
X_1, X_2, A_1, R, R_4 and R_5 are such as previously defined in the summary of the invention; and

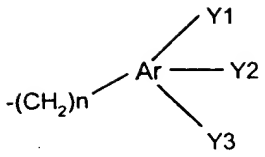
- when X_1 and X_2 represent hydrogen, R is not alkyl, phenyl, benzyl or allyl ,
- when X_1 represents hydrogen and X_2 represents 7-Cl or CH_3, R is not alkyl ; and
- when X_1 represents hydrogen, X_2 is not 8-Cl.

The invention relates also to a group of a formula I or II compounds particularly active as TNFα inhibitors and in which :

- A_1 is O or S ;
- X_1 and X_2, similar or different, represent :
  - hydrogen, hydroxy, halogen, amino, nitro, mercapto, cyano, carboxy,
  - lower alkyl, lower alkoxy or $-S(O)_mR_8$ in which m is 0, 1 or 2 and R_8 is lower alkyl, possibly substituted by one or several halogen atoms.
- In a preferred manner, X_1 is H and X_2 is halogen, notably 7-Br, or lower alkyl, notably 7-CH_3.

- R represents:





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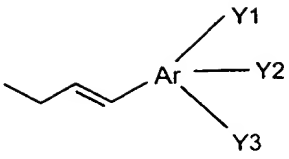


in which :

- n is an integer from 1 to 5,
- Ar is an aromatic cycle including 5 or 6 atoms with 0 to 3 heteroatoms chosen among O, S or N,
- Y1, Y2 and Y3, similar or different represent :
  - hydrogen, hydroxy, mercapto, amino, nitro, halogen, $-(CH_2)_sCO-Q_1-Q_2-Q_3$, $(CH_2)_s-CN$ in which s is an integer from 0 to 6 ;
  - lower alkyl, lower alkoxy or $-S(O)_mR_8$ in which m is 0, 1 or 2 and R_8 is a lower alkyl, possibly substituted by one or several halogen atoms.

The substituents particularly preferred forming the group R include cinnamyl, 3-pyridyl allyl, paracyano benzyl, dimethoxy benzyl and 3-pyridyl méthyl.

- R_4 and R_5, similar or different, represent :
  lower alkyl, R_4 and R_5 being able to be linked to form a saturated cycle or including one or several double-bonds with one or several heteroatoms chosen among O, S or N and possibly bridged by a lower alkyl, dialkylated gem or substituted by one or several groups chosen among hydroxy, keto, lower alkyl, lower alkoxy, phenyl alkyl or $CO-Q_1-Q_2-Q_3$. substituants particularly preferred forming the group NR_4R_5 include dimethylamino, pyrrolidine and azepanyl.

Compounds particularly preferred as TNFα inhibitors include the following molecules :

3	7-Bromo-1-dimethylamino-4-((E)-3-pyridin-3-yl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
104	1-Dimethylamino-7-methyl-4-(3-pyridin-3-yl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
94	4-(3,4-Dimethoxy-benzyl)-7-methyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
101	4-(1-Dimethylamino-7-methyl-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile
85	7-Bromo-1-dimethylamino-4-(3-phenyl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
98	7-Methyl-4-(3-phenyl-allyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
79	4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile
91	1-Azepan-1-yl-7-methyl-4-pyridin-3-ylmethyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
93	4-(7-Methyl-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile
103	1-Dimethylamino-7-methyl-4-((E)-3-phenyl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
46	4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile
35	1-Azepan-1-yl-7-bromo-4-(3,4-dimethoxy-benzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

Among the groups defined above, the following substituents are particularly preferred :

- In a general manner for groups X_1, X_2, X_3, X_4, R, R_1, R_2, R_3, R_4, R_5 :
  - halogen : F, Cl, Br, I, preferably Br and Cl,
  - lower alkyl : linear or branched including 1 to 6, preferably 1 to 3 carbon atoms,
  - lower alkoxy : linear or branched comprising from 1 to 5, preferably 1 to 3 carbon atoms,
  - lower alkylthio : linear or branched comprising from 1 to 5, preferably 1 to 3 carbon atoms,

- lower alcenyl : comprising from 3 to 6, preferably 3 to 4 carbon atoms, more particularly allyl ,
- lower alkynyl : comprising from 3 to 9 carbon atoms, more particularly propargyl and phényl-propargyl ,
- 2-, 3- or 4-pyridylalkyl in which alkyl includes from 1 to 5, preferably 1 to 3 carbon atoms,
- aryl : comprising from 5 to 8, preferably 5 or 6 atoms,
- aralkyl in which alkyl includes from 1 to 6, preferably 1 to 4 carbon atoms,
- cycloalkyl : including 3 to 8, preferably 3 to 6 carbon atoms,
- cycloalkyl alkyl in which alkyl includes from 1 to 6, preferably 1 to 3 atoms de carbone and cycloalkyl include from 3 to 8, de preferably 3 to 6 carbon atoms ,
- lower alkyl, lower alkoxy or lower alkylthio possibly substituted by one or several halogen atoms : we will prefer trisubstituted groups of type $-(CH_2)_p-CF_3$, $-O-(CH_2)_p-CF_3$ or $-S-(CH_2)_p-CF_3$, in which p is an integer from 0 to 3.

- In particular manner for the groups X_1 and X_2 :
- $-NH-R_1$, or $-NR_2R_3$: when lower alkyl is substituted by one or several groups chosen among halogen, hydroxy, cyano, lower alkoxy or $CO-Q_1-Q_2-Q_3$, the substituents number varies between 1 and 4, preferably between 1 and 2,
- $-NR_2R_3$: when R_2 and R_3 are bound to form a cycle, this cycle is characterized as including preferably :
- between 1 and 4, more particularly between 1 and 2 heteroatoms chosen among O, S or N, the cyclic substituents of this type being, in a preferred manner, saturated cycles of type C_mN in which m is an integer from 2 to 7, preferably 4 to 6, particularly preferred cycles being chosen among group including pyrrolidine, piperidine, homopiperidine or cyclooctylamine and
- between 0 and 4, in a preferred manner between 0 and 2, more particularly between 1 and 2 substituents chosen among hydroxy, keto, lower alkyl, lower alkoxy or $-CO-Q_1-Q_2-Q_3$,
- groups X_1 and X_2 are particularly localized in position 7 and 8 of aromatic cycle for formula I and II compounds to which they are bound.

- In particular manner for the group R :

- the substituents Y1, Y2 and Y3 are particularly localized in position 3 and/or 4 of the aromatic cycle to which they are bound.

- In particular manner for the groups R_4 and R_5 :
- when R_4 and R_5 are bound to form a cycle, this cycle is characterized as preferably including :
- between 1 and 4 heteroatoms chosen among O, S or N, cyclic substituents of this type being, in a preferred manner, saturated cycles of type C_mN, m being an integer between 2 and 7, cycles particularly preferred being chosen among group including pyrrolidine, piperidine, homopiperidine or cyclooctylamine, and
- between 0 and 4, in a preferred manner between 0 and 2 substituents chosen among hydroxy, keto, lower alkyl, lower alkoxy or $-CO-Q_1-Q_2-Q_3$.

Among the preferred compounds of the current invention, we find the following compounds :

1 1-(Azepan-1-yl)-7-chloro-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

2 1-(azepan-1-yl)-7-chloro-3-(3-phenylallyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

3 7-Bromo-1-dimethylamino-4-((E)-3-pyridin-3-yl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4 7-Bromo-4-pyridin-3-ylmethyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

5 7-Bromo-3-pyridin-3-ylmethyl-1-pyrrolidin-1-yl-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

6 1-Azepan-1-yl-4-(3-phenyl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7 1-(azepan-1-yl)-7-chloro-4-allyl-4H-[1,2,4]triazolo[4,3-a]- quinazolin-5-one

8 1-(azepan-1-yl)-7-chloro-4-(4-methylbenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

9 1-(azepan-1-yl)-7-chloro-4-(2-chlorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

10 1-(azepan-1-yl)-7-chloro-4-(3-chlorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

11 1-(azepan-1-yl)-7-chloro-4-(4-chlorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

12 1-(azepan-1-yl)-7-chloro-4-(4-bromobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

13 1-(azepan-1-yl)-7-chloro-4-(4-fluorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

14 1-(azepan-1-yl)-7-chloro-4-(4-(trifluoromethyl)benzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

15 1-(azepan-1-yl)-7-chloro-4-(4-cyanobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

16 1-(azepan-1-yl)-7-chloro-4-(2-methoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

17 1-(azepan-1-yl)-7-chloro-4-(3-methoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

18 1-(azepan-1-yl)-7-chloro-4-(4-methoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

19 1-(azepan-1-yl)-7-chloro-4-(3,4-dichlorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

20 1-(azepan-1-yl)-7-chloro-4-(3,4-dimethoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

21 1-(azepan-1-yl)-7-chloro-4-(2-pyridylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

22 1-(azepan-1-yl)-7-chloro-4-(3-pyridylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

23 1-(azepan-1-yl)-7-chloro-4-(4-pyridylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

24 1-(azepan-1-yl)-7-chloro-4-(2-phenylthyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

25 1-(azepan-1-yl)-7-chloro-4-[2-(4-methoxyphenyl)ethyl]-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

26 1-(azepan-1-yl)-7-chloro-4-(3-phenylpropyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

27 1-Azepan-1-yl-7-chloro-4-(2-oxo-2-phenyl-ethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

28 1-(azepan-1-yl)-7-chloro-4-[2-(4-methoxyphenyl)-2-oxoethyl]-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

29 1-(azepan-1-yl)-7-chloro-4-[2-(4-chlorophenyl)-2-oxoethyl]-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

30 5-[(1-(azepan-1-yl)-7-chloro-5-oxo-5H-[1,2,4]triazolo[4,3-a]-quinazolin-4-yl)acetyl]-2-methoxybenzoic acid methyl ester

31 7-Chloro-4-pyridin-3-ylmethyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

32 1-(azepan-1-yl)-7-bromo-4-(4-chloro-benzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

33 1-Azepan-1-yl-7-bromo-4-(4-fluoro-benzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

34 4-(1-Azepan-1-yl-7-bromo-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

35 1-Azepan-1-yl-7-bromo-4-(3,4-dimethoxy-benzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

36 1-(azepan-1-yl)-7-bromo-4-(3-pyridinylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

37 1-(azepan-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

38 1-Azepan-1-yl-7-bromo-4-[3-(4-chloro-phenyl)-allyl]-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

39 1-Azepan-1-yl-7-bromo-4-[3-(4-methoxy-phenyl)-allyl]-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

40 1-Azepan-1-yl-7-bromo-4-((E)-3-pyridin-3-yl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

41 1-Azepan-1-yl-7-bromo-4-(3-pyridin-4-yl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

42 7-Bromo-4-(4-methyl-benzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

43 7-Bromo-4-(4-chloro-benzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

44 7-Bromo-4-(4-fluoro-benzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

45 3-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

46 4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

47 4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzoic acid methyl ester

48 7-Bromo-4-(4-nitro-benzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

49 7-Bromo-4-(4-methoxy-benzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

50 Acetic acid 4-(7-bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl ester

51 7-Bromo-4-(4-hydroxy-benzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

52 7-Bromo-4-(3,4-dimethoxy-benzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

53 4-Benzo[1,3]dioxol-5-ylmethyl-7-bromo-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

54 7-Bromo-4-(3,5-dimethoxy-benzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

55 7-Bromo-1-pyrrolidin-1-yl-4-(3,4,5-trimethoxy-benzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

56 [4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-acetic acid

57 1-(pyrrolidin-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

58 7-Bromo-4-(3-phenyl-allyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

59 7-Bromo-4-[(E)-3-(4-chloro-phenyl)-allyl]-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

60 7-Bromo-4-[3-(4-methoxy-phenyl)-allyl]-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

61 7-Bromo-4-(3-pyridin-3-yl-allyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

62 7-Bromo-4-((E)-3-pyridin-4-yl-allyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

63 7-Bromo-4-(1H-imidazol-4-ylmethyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

64 7-Bromo-4-(3,5-dimethyl-isoxazol-4-ylmethyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

65 7-Bromo-4-cyclopentylmethyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

66 7-Bromo-4-butyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

67 7-Bromo-1-pyrrolidin-1-yl-4-(2,2,2-trifluoro-ethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

68 7-Bromo-4-(2-hydroxy-ethyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

69 7-Bromo-4-(2-diethylamino-ethyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

70 7-Bromo-4-prop-2-ynyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

71 7-Bromo-4-(2-phenoxy-ethyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

72 7-Bromo-4-(2-phenylsulfényl-ethyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

73 (7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-yl)-phenyl-acetic acid methyl ester

74 4-(7-Bromo-5-oxo-1-piperidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

75 7-Bromo-4-(3,4-dimethoxy-benzyl)-1-piperidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

76 1-(piperidin-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

77 7-Bromo-4-(3-pyridin-3-yl-allyl)-1-thiomorpholin-4-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

78 Bromo-dimethylamino-(4-methyl-benzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

79 4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

80 7-Bromo-1-dimethylamino-4-(4-hydroxy-benzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

81 4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzoic acid methyl ester

82 [4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-acetic acid

83 [4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-acetonitrile

84 7-Bromo-1-dimethylamino-4-pyridin-3-ylmethyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

85 7-Bromo-1-dimethylamino-4-(3-phenyl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

86 7-Bromo-1-dimethylamino-4-(3-phenyl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

87 7-Bromo-1-dimethylamino-4-(3-pyridin-4-yl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

88 7-Bromo-1-dimethylamino-4-prop-2-ynyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

89 7-Bromo-1-dimethylamino-4-(3-phenyl-prop-2-ynyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

90 (7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-yl)-phenyl-acetic acid methyl ester

91 1-Azepan-1-yl-7-methyl-4-pyridin-3-ylmethyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

92 1-Azepan-1-yl-7-methyl-4-(3-phenyl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

93 4-(7-Methyl-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

94 4-(3,4-Dimethoxy-benzyl)-7-methyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

95 4-(7-Methyl-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzoic acid methyl ester

96 [4-(7-Methyl-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-acetic acid

97 7-Methyl-4-pyridin-3-ylmethyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

98 7-Methyl-4-(3-phenyl-allyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

99 [4-(7-Methyl-5-oxo-1-thiomorpholin-4-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-acetic acid

100 7-Methyl-4-(3-pyridin-3-yl-allyl)-1-thiomorpholin-4-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

101 4-(1-Dimethylamino-7-methyl-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

102 [4-(1-Dimethylamino-7-methyl-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-acetic acid

103 1-Dimethylamino-7-methyl-4-((E)-3-phenyl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

104 1-Dimethylamino-7-methyl-4-(3-pyridin-3-yl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

105 1-Dimethylamino-7-methyl-4-(3-pyridin-4-yl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

106 1-(azepan-1-yl)-8-methyl-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

107 4-(4-Cyano-benzyl)-1-dimethylamino-5-oxo-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinazoline-7-carbonitrile

108 7-Hydroxy-4-((E)-3-phenyl-allyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

109 1-(azepan-1-yl)-3-(3-phenylallyl)- 3H-[1,2,4]triazolo[4,3-a]- quinazolin-5-one

110 3-Allyl-1-azepan-1-yl-7-chloro-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

111 1-(azepan-1-yl)-7-chloro-3-benzyl-3H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

112 1-Azepan-1-yl-7-chloro-3-(4-methyl-benzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

113 1-(azepan-1-yl)-7-chloro-3-(2-chlorobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

114 1-(azepan-1-yl)-7-chloro-3-(3-chlorobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

115 1-(azepan-1-yl)-7-chloro-3-(4-chlorobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

116 1-(azepan-1-yl)-7-chloro-3-(4-bromobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

117 1-(azepan-1-yl)-7-chloro-3-(4-fluorobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

118 1-(azepan-1-yl)-7-chloro-3-(4-(trifluoromethyl)benzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

119 1-(azepan-1-yl)-7-chloro-3-(4-cyanobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

120 1-(azepan-1-yl)-7-chloro-3-(2-methoxybenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

121 1-(azepan-1-yl)-7-chloro-3-(3-methoxybenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

122 1-(azepan-1-yl)-7-chloro-3-(4-methoxybenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

123 1-(azepan-1-yl)-7-chloro-3-(3,4-dichlorobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

124 1-(azepan-1-yl)-7-chloro-3-(3,4-dimethoxybenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

125 1-(azepan-1-yl)-7-chloro-3-(2-pyridylmethyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

126 1-(azepan-1-yl)-7-chloro-3-(3-pyridylmethyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

127 1-(azepan-1-yl)-7-chloro-3-(2-phenylthyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

128 1-(azepan-1-yl)-7-chloro-3-[2-(4-methoxyphenyl)ethyl]-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

129 1-(azepan-1-yl)-7-chloro-3-(3-phenylpropyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

130 1-Azepan-1-yl-7-chloro-3-(2-oxo-2-phenyl-ethyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

131 1-(azepan-1-yl)-7-chloro-3-[2-(4-methoxyphenyl)-2-oxoethyl]-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

132 1-(azepan-1-yl)-7-chloro-3-[2-(4-chlorophenyl)-2-oxoethyl]-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

133 5-[(1-(azepan-1-yl)-7-chloro-5-oxo-5H-[1,2,4]triazolo[4,3-a]-quinazolin-3-yl)acetyl]-2-methoxybenzoic acid methyl ester

134 1-(azepan-1-yl)-7-bromo-3-(4-chlorobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

135 1-(azepan-1-yl)-7-bromo-3-(4-fluorobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

136 4-(1-(azepan-1-yl)-7-bromo-5-oxo-5H-[1,2,4]triazolo[4,3-a]- quinazolin-3-ylmethyl)- benzonitrile

137 1-(azepan-1-yl)-7-bromo-3-(3,4-dimethoxybenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

138 [4-(7-Bromo-5-oxo-1-perhydro-azepin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-3-ylmethyl)-phenyl]-acetic acid

139 1-(azepan-1-yl)-7-bromo-3-(pyridin-3-ylmethyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

140 1-Azepan-1-yl-7-bromo-3-((E)-3-phenyl-allyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

141 7-Bromo-3-((E)-3-phenyl-allyl)-1-piperidin-1-yl-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

142 7-bromo-3-(4-chlorobenzyl)-1-(pyrrolidin-1-yl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

143 7-bromo-3-(4-fluorobenzyl)-1-(pyrrolidin-1-yl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

144 4-(7-bromo-5-oxo-1-(pyrrolidin-1-yl)-5H-[1,2,4]triazolo[4,3-a]-quinazolin-3-ylmethyl)- benzonitrile

145 4-(7-bromo-5-oxo-1-(pyrrolidin-1-yl)-5H-[1,2,4]triazolo[4,3-a]-quinazolin-3-ylmethyl)benzoic acid methyl ester

146 7-Bromo-3-(4-methoxy-benzyl)-1-pyrrolidin-1-yl-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

147 Acetic acid 4-(7-bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-3-ylmethyl)-phenyl ester

148 7-Bromo-1-dimethylamino-3-(4-hydroxy-benzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

149 3-(benzo[1,3]dioxol-5-ylmethyl)-7-bromo-1-(pyrrolidin-1-yl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

150 7-bromo-3-(3,5-dimethoxy-benzyl)-1-(pyrrolidin-1-yl)-3H-[1,2,4]triazolo- [4,3-a]quinazolin-5-one

151 7-bromo-1-(pyrrolidin-1-yl)-3-(3,4,5-trimethoxybenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

152 7-Bromo-3-(1H-imidazol-4-ylmethyl)-1-pyrrolidin-1-yl-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

153 7-bromo-3-(n-butyl)-1-(pyrrolidin-1-yl)-3H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

154 (7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-3-yl)-phenyl-acetic acid methyl ester

155 7-Bromo-1-dimethylamino-3-(3-phenyl-allyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

156 (7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-3-yl)-phenyl-acetic acid methyl ester

157 1-(azepan-1-yl)-7-methyl-3-(3-phenylallyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

158 7-methyl-3-(3-phenylallyl)-1-(pyrrolidin-1-yl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

159 1-(azepan-1-yl)-3,8-dimethyl-3H-[1,2,4]triazolo[4,3-a]- quinazolin-5-one

160 1-Azepan-1-yl-8-methyl-3-((E)-3-phenyl-allyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

161 7-hydroxy-3-(3-phenylallyl)-1-(pyrrolidin-1-yl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-
5-one

162 1,8-bis(azepan-1-yl)-3-(3-phenylallyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

163 1-(azepan-1-yl)-4-benzyl-7-bromo-4H-[1,2,4]triazolo[4,3-a]- quinazolin-5-one

164 4-benzyl-7-bromo-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

165 4-Benzyl-7-bromo-1-(butyl-methyl-amino)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

166 4-benzyl-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

167 7-chloro-1-dibutylamino-4-methyl-4H-[1,2,4]triazolo[4,3-a]- quinazolin-5-one

168 7-chloro-4-methyl-1-(piperidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

169 7-Chloro-4-methyl-1-(4-methyl-piperazin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

170 7-Chloro-4-methyl-1-(1,8,8-trimethyl-3-aza-bicyclo[3.2.1]oct-3-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

171 1-(azepan-1-yl)-7-chloro-4-phenyl-4H-[1,2,4]triazolo[4,3-a]- quinazolin-5-one

172 1-(azepan-1-yl)-4-benzyl-7-chloro-4H-[1,2,4]triazolo[4,3-a]- quinazolin-5-one

173 4-benzyl-7-chloro-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

174 4-benzyl-7-chloro-1-(piperidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

175 1-(azepan-1-yl)-8-chloro-4-methyl-4H-[1,2,4]triazolo[4,3-a]- quinazolin-5-one

176 1-(azepan-1-yl)-4-benzyl-8-chloro-4H-[1,2,4]triazolo[4,3-a]- quinazolin-5-one

177 1-(azepan-1-yl)-7-bromo-4-methyl-4H-[1,2,4]triazolo[4,3-a]- quinazolin-5-one

178 4-benzyl-7-bromo-1-(piperidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

179 4-Benzyl-7-bromo-1-dimethylamino-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

180 4-Benzyl-7-bromo-1-morpholin-4-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

181 4-Benzyl-7-bromo-1-thiomorpholin-4-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

182 4-Benzyl-7-bromo-1-(4-methyl-piperazin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

183 4-Benzyl-7-bromo-1-(4-phenyl-piperazin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

184 4-Benzyl-1-(4-benzyl-piperazin-1-yl)-7-bromo-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

185 4-Benzyl-7-bromo-1-(3,6-dihydro-2H-pyridin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

186 4-Benzyl-7-bromo-1-(2,5-dihydro-pyrrol-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

187 4-Benzyl-7-bromo-1-(3-hydroxy-pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

188 4-Benzyl-7-bromo-1-methylamino-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

189 4-Benzyl-7-iodo-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

190 1-Azepan-1-yl-4-benzyl-7-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

191 4-Benzyl-7-methyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

192 4-Benzyl-1-dimethylamino-7-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

193 4-Benzyl-7-methyl-1-thiomorpholin-4-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

194 1-Azepan-1-yl-4-benzyl-8-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

195 1-Azepan-1-yl-4-benzyl-7-methoxy-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

196 4-Benzyl-7-methoxy-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

197 4-Benzyl-5-oxo-1-pyrrolidin-1-yl-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinazoline-7-carbonitrile

198 1-Azepan-1-yl-4-benzyl-7-nitro-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

199 1-(azepan-1-yl)-4-benzyl-7-chloro-4H-[1,2,4]triazolo[4,3-a]- quinazolin-5-one

200 1-(azepan-1-yl)-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

201 1-(azepan-1-yl)-4-benzyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

202 1-(azepan-1-yl)-6-chloro-4-methyl-4H-[1,2,4]triazolo[4,3-a]- quinazolin-5-one

203 1-(azepan-1-yl)-7-chloro-4-methyl-4H-[1,2,4]triazolo[4,3-a]- quinazolin-5-one

204 1-(azepan-1-yl)-7-chloro-4-ethyl-4H-[1,2,4]triazolo[4,3-a]- quinazolin-5-one

205 7-chloro-4-methyl-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

206 7-chloro-4-methyl-1-(morpholin-4-yl)-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

207 1-(azocan-1-yl)-7-chloro-4-methyl-4H-[1,2,4]triazolo[4,3-a]- quinazolin-5-one

208 7-chloro-1-(3,4-dihydro-2H-quinolin-1-yl)-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

209 7-chloro-1-(3,4-dihydro-1H-isoquinolin-2-yl)-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

210 1-(4-benzylpiperidin-1-yl)-7-chloro-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

211 7-chloro-4-methyl-1-(1,3,3-trimethyl-6-azabicyclo[3,2,1]oct-6-yl)-4H-[1,2,4]triazolo[4,3-a]- quinazolin-5-one

212 1-(azepan-1-yl)-7-fluoro-4-methyl-4H-[1,2,4]triazolo[4,3-a]- quinazolin-5-one

213 1-(azepan-1-yl)-7-iodo-4-methyl-4H-[1,2,4]triazolo[4,3-a]- quinazolin-5-one

214 1-(azepan-1-yl)-7-methoxy-4-methyl-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

215 4-Benzyl-7-bromo-1-(ethyl-methyl-amino)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

216 4-Benzyl-1-diethylamino-7-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

217 4-Benzyl-7-bromo-1-pyrrol-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

218 4-(4-Amino-benzyl)-7-bromo-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

219 4-Benzyl-7-hydroxy-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

220 4-(7-Hydroxy-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

221 N-(4-Benzyl-5-oxo-1-pyrrolidin-1-yl-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinazolin-7-yl)-acetamide

222 N-[5-Oxo-4-(3-phenyl-allyl)-1-pyrrolidin-1-yl-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinazolin-7-yl]-acetamide

223 7-Amino-4-((E)-3-phenyl-allyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

224 7-Amino-1-azepan-1-yl-4-benzyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

225 7-Amino-4-benzyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

226 4-(7-Amino-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

227 7-Amino-4-((E)-3-pyridin-3-yl-allyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

228 4-(7-Amino-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

229 7-Amino-1-dimethylamino-4-((E)-3-phenyl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

230 4-Benzyl-7-methylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

231 4-(7-Methylamino-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

232 4-Benzyl-8-methylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

233 4-Benzyl-7-ethylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

234 4-Benzyl-7-isopropylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

235 N-(4-Benzyl-5-oxo-1-pyrrolidin-1-yl-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinazolin-7-yl)-methanesulfonamide

236 4-Benzyl-7-dimethylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

237 4-Benzyl-1-dimethylamino-5-oxo-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinazoline-7-carbonitrile

238 4-Benzyl-5-oxo-1-pyrrolidin-1-yl-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinazoline-7-carboxylic acid

239 [4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-acetic acid methyl ester

240 2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-N-methyl-acetamide

241 2-[4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-acetamide

242 2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-N,N-dimethyl-acetamide

243 2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-N-hydroxy-acetamide

244 4-(1-Dimethylamino-7-methyl-5-thioxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

245 4-(7-Bromo-1-dimethylamino-5-thioxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

246 1-Dimethylamino-7-methyl-4-(3-pyridin-3-yl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazoline-5-thione

247 4-benzyl-7-(N,N-dimethylsulfonylamino)-1-(pyrrolidin-1-yl) -4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one

Among the compounds mentioned above, the following compounds are preferred :

1	1-(Azepan-1-yl)-7-chloro-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
3	7-Bromo-1-dimethylamino-4-((E)-3-pyridin-3-yl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
11	1-(azepan-1-yl)-7-chloro-4-(4-chlorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
13	1-(azepan-1-yl)-7-chloro-4-(4-fluorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
20	1-(azepan-1-yl)-7-chloro-4-(3,4-dimethoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
22	1-(azepan-1-yl)-7-chloro-4-(3-pyridylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
32	1-(azepan-1-yl)-7-bromo-4-(4-chlorophenylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
34	4-(1-Azepan-1-yl-7-bromo-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile
35	1-Azepan-1-yl-7-bromo-4-(3,4-dimethoxy-benzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
37	1-(azepan-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
40	1-Azepan-1-yl-7-bromo-4-((E)-3-pyridin-3-yl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
41	1-Azepan-1-yl-7-bromo-4-(3-pyridin-4-yl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
42	7-Bromo-4-(4-methyl-benzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
43	7-Bromo-4-(4-chloro-benzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
44	7-Bromo-4-(4-fluoro-benzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
46	4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile
47	4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzoic acid methyl ester

48 7-Bromo-4-(4-nitro-benzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

49 7-Bromo-4-(4-methoxy-benzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

50 Acetic acid 4-(7-bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl ester

51 7-Bromo-4-(4-hydroxy-benzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

52 7-Bromo-4-(3,4-dimethoxy-benzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

57 1-(pyrrolidin-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

59 7-Bromo-4-[(E)-3-(4-chloro-phenyl)-allyl]-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

60 7-Bromo-4-[3-(4-methoxy-phenyl)-allyl]-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

61 7-Bromo-4-(3-pyridin-3-yl-allyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

62 7-Bromo-4-((E)-3-pyridin-4-yl-allyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

75 7-Bromo-4-(3,4-dimethoxy-benzyl)-1-piperidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

76 1-(piperidin-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

78 7-Bromo-1-dimethylamino-4-(4-methyl-benzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

79 4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

80 7-Bromo-1-dimethylamino-4-(4-hydroxy-benzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

81 4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzoic acid methyl ester

83 [4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-acetonitrile

85	7-Bromo-1-dimethylamino-4-(3-phenyl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
89	7-Bromo-1-dimethylamino-4-(3-phenyl-prop-2-ynyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
92	1-Azepan-1-yl-7-methyl-4-(3-phenyl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
94	4-(3,4-Dimethoxy-benzyl)-7-methyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
96	[4-(7-Methyl-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-acetic acid
98	7-Methyl-4-(3-phenyl-allyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
102	[4-(1-Dimethylamino-7-methyl-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-acetic acid
103	1-Dimethylamino-7-methyl-4-((E)-3-phenyl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
104	1-Dimethylamino-7-methyl-4-(3-pyridin-3-yl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
138	[4-(7-Bromo-5-oxo-1-perhydro-azepin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-3-ylmethyl)-phenyl]-acetic acid
164	4-benzyl-7-bromo-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one
186	4-Benzyl-7-bromo-1-(2,5-dihydro-pyrrol-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
189	4-Benzyl-7-iodo-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
190	1-Azepan-1-yl-4-benzyl-7-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
218	4-(4-Amino-benzyl)-7-bromo-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
223	7-Amino-4-((E)-3-phenyl-allyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
224	7-Amino-1-azepan-1-yl-4-benzyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

227 7-Amino-4-((E)-3-pyridin-3-yl-allyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

229 7-Amino-1-dimethylamino-4-((E)-3-phenyl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

230 4-Benzyl-7-methylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

231 4-(7-Methylamino-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

232 4-Benzyl-8-methylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

233 4-Benzyl-7-ethylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

234 4-Benzyl-7-isopropylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

239 [4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-acetic acid methyl ester

240 2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-N-methyl-acetamide

241 2-[4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-acetamide

242 2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-N,N-dimethyl-acetamide

243 2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-N-hydroxy-acetamide

246 1-Dimethylamino-7-methyl-4-(3-pyridin-3-yl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazoline-5-thione

Among the compounds mentioned above, the following compounds are preferred :

3	7-Bromo-1-dimethylamino-4-((E)-3-pyridin-3-yl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
20	1-(azepan-1-yl)-7-chloro-4-(3,4-dimethoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
22	1-(azepan-1-yl)-7-chloro-4-(3-pyridylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
34	4-(1-Azepan-1-yl-7-bromo-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile
35	1-Azepan-1-yl-7-bromo-4-(3,4-dimethoxy-benzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
37	1-(azepan-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
40	1-Azepan-1-yl-7-bromo-4-((E)-3-pyridin-3-yl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
41	1-Azepan-1-yl-7-bromo-4-(3-pyridin-4-yl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
42	7-Bromo-4-(4-methyl-benzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
43	7-Bromo-4-(4-chloro-benzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
52	7-Bromo-4-(3,4-dimethoxy-benzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
57	1-(pyrrolidin-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
61	7-Bromo-4-(3-pyridin-3-yl-allyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
76	1-(piperidin-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
79	4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile
81	4-(Bromo-dimethylamino-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzoic acid methyl ester
85	7-Bromo-1-dimethylamino-4-(3-phenyl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

89 7-Bromo-1-dimethylamino-4-(3-phenyl-prop-2-ynyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

92 1-Azepan-1-yl-7-methyl-4-(3-phenyl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

94 4-(3,4-Dimethoxy-benzyl)-7-methyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

98 7-Methyl-4-(3-phenyl-allyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

223 7-Amino-4-((E)-3-phenyl-allyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

227 7-Amino-4-((E)-3-pyridin-3-yl-allyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

230 4-Benzyl-7-methylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

231 4-(7-Methylamino-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

239 [4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-acetic acid methyl ester

240 2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-N-methyl-acetamide

242 2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-N,N-dimethyl-acetamide

246 1-Dimethylamino-7-methyl-4-(3-pyridin-3-yl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazoline-5-thione

The invention relates also to salts acceptable in pharmacy of a formula I or II compounds. We will find a review of pharmacologically acceptable salts in J. Pharm. Sci., 1977, 66, 1-19. However, by a pharmacologically acceptable salt of a formula I or II compound presenting a basic function, we mean the addition salt of a formula I or II compounds from non toxic inorganic or organic acids as for example salts of hydrobromic, hydrochloric, sulfuric, phosphoric, nitric, acetic, succinic, tartric, citric, maleic, hydroxymaleic, benzoic, fumaric, toluene-sulfonic, isethionic acids and others. Various salts of quaternary ammonium of I or II formula are also included in category compounds of this invention. And by pharmacologically

acceptable salts of a formula I or II compound presenting an acid function, we mean usual salts of a formula I or II compounds made from non-toxic mineral or organic bases as for example hydroxides of alkaline and alkaline earth metals (sodium, potassium, magnesium and calcium), amines (dibenzylethtylnediamine, trimethylamine, piperidine, pyrrolidine, benzylamine and others) or also quaternary ammonium hydroxides like tetramethylammonium hydroxide.

As previously mentioned, formula I and II compounds of the current invention are inhibitors of phosphodiesterase enzyme and particularly of phosphodiesterase 4 (PDE4) enzyme.

Consequently, their use is recommended for treatment of diseases or affections relying on therapy by PDE4 inhibition. As an example, compounds of the current invention can be recommended for treatment of septicemia, polyvisceral deficiency, asthma, chronic bronchitis, emphysema, chronic obstructive pneumopathy (or COPD), allergic rhinitis, atopic dermatitis, pulmonary high blood pressure, cardiac or pulmonary insufficiency, congestive cardiac insufficiency, psoriasis, inflammatory diseases of the digestive system such as hemorrhagic rectocolitis and Crohn's disease, diseases linked to elevated TNF-α levels such as acute respiratory distress syndrome in the adult and acute pancreatitis, rhumatoid arthritis, osteoporosis, multiple sclerosis and depression.

PDE4 inhibitors of the current invention may also be used for treatment of acute pulmonary attack, neuronal attack caused by ischemia (ischemia-induced neuronal damage), diabetes, chronic lymphoid leukemia, and to attenuate development of tolerance or dependence phenomena to morphine. Compounds of the invention may also contribute to decreasing memory loss of behavior (behavioral memory) such as observed for example in patients suffering from Alzheimer's disease.

We may also consider use of the compounds of the current invention in the fields of urology, more particularly in treatment of prostate disease such as benign hypertrophy of the prostate or for prevention of premature child birth, for example by inhibition of contraction triggering before term, preferably by PDE4 inhibitor action on myometrium.

Structure-activity analysis of formula I and II compounds

The inventors, wishing not to be bound in a formal manner to a definitive theory, agree that structural parameters mentioned below may be considered in order to guide the person skilled in the art in the choice of substituents combination which, beyond preferred compounds disclosed in the current application, may allow not only an optimization of the PDE4 inhibitor

activity, but also a better optimization of important additional parameters such as solubility, biodisposability and toxicity of considered compounds.

First, the inventors consider that the catalytic site of the enzyme PDE4 is of a sufficiently large size to globally accommodate a fairly wide range of structural changes in substituents of the compounds of the invention which can bind to this site. In this respect, the inventors consider that compounds of the current invention have probably the capacity to interact at least on three distinct points of the catalytic site of the isoenzyme PDE4. One first interaction point may be localized on the aromatic ring including the substituents X_1 and X_2. A second interaction point is probably localized on substituent R while a third interaction point is probably localized on group NR_4R_5. Potential functionality of each binding point is suggested below.

However, it is important to precise here that interaction points mentioned above are not necessarily classified by increasing or decreasing importance order relating to their incidence on inhibitory activity of invention compounds. In fact, it seems possible that each interaction point participates in a different manner in global pharmacological properties of these compounds.

The first interaction point mentioned previously may be localized then on the aromatic ring including substituents X_1 and X_2. This aromatic ring may participate to the invention compound binding to enzyme PDE4 catalytic site, it seems possible to modulate this binding by substituents X_1 and X_2 choice.

Experiments performed up-to-date by the inventors tend to demonstrate that substituents X_1 and X_2 currently preferred are those for which X_1 is hydrogen and X_2 is chosen among halogen, more particularly Br and Cl, methyl, hydroxy, amino and alkylamino. We establish then that among preferred substituents X_2, we simultaneously find some donors (e.g. methyl) and some attractors (e.g. Br, Cl) of electrons. It seems then unlikely that X_2 could be chosen solely according to electronic properties of the recommended substituent. The inventors agree that important selection criteria are placed initially on substituent position in the aromatic ring and therefore on the level of some parameters such as substituent steric congestion or presence of donor atom or proton acceptor.

However, it seems established that substituents X_1 and X_2 position on the aromatic ring could have an influence on final activity of invention compounds. As an example, compounds including a substituent other than hydrogen in position 7 are generally more active that the same compounds including this substituent in position 8. Thus it seems probable than choice and position of substituents X_1 and X_2 allow to move the aromatic ring inside the cavity of the PDE4 catalytic site and consequently to modulate inhibitory activity of invention compounds. Moreover, it seems that compounds including a substituent in position 7 are more selective of sub-type PDE4 compared to the other isoenzymes PDE5, PDE3 and PDE1 than compounds including a substituent in position 8. These latter have a PDE4 inhibitory activity (although less) but they seem less selective compared to the other isoenzymes. However, it seems clearly also that although X_1 and X_2 could be chosen among an outstanding number of substituents, we will obtain a better tolerance for this choice if substituent R is well targeted.

The second interaction point of compounds of the current invention with the enzyme PDE4 will be localized on the substituent R. The inventors reckon that it concerns presumably of the most important anchorage point of the molecule to the enzyme. It seems indeed probable that this second interaction is localized in a large cavity inside the PDE4 catalytic site. It is then essential that the substituent R can be anchored to the catalytic site. However, the choice of groups included in the definition of R given above, seems to demonstrate some flexibility on R anchorage to this second binding site. Therefore, it could be possible to obtain a PDE4 inhibitory activity with compounds having rather different substituents R from a structural point of view. As an example, we will prefer the use of a substituent including an aromatic ring, preferably substituted itself, and separated from the principal heterocycle by a chain including between 1 and 4 atoms, particularly some carbon atoms, the said substituent presenting a relatively variable spatial orientation. This observation seems to open the way to the possibility to modulate in a more subtle manner the global properties of invention compounds.

The inventors agree indeed that although substituent R remains most probably a determinant element on PDE4 inhibitory activity of invention compounds, it is probably possible to make it vary and then act on the important extra pharmacological parameters without altering this inhibitory activity in a substantial manner. As an example, some compounds including in substituent R a group $-CH_2CH = CH-C_6H_5$ or a substituted benzyl group, preferably in

position 4 (other substituents being identical for the two compounds), have PDE4 inhibitory activity of same magnitude order.

The third interaction site of the compounds of the invention on PDE4 is localized presumably on group $-NR_4R_5$. The inventors agree that it concerns probably a binding site much more specific that the two sites disclosed above although substituent R moving in the enzymatic cavity may however influence on specificity of this third site. Compounds of the invention having the best inhibitory activities are those for which R_4 and R_5, which represent each a lower alkyl, are bound to form a cycle, preferably including between 5 and 8 carbon atoms, more particularly a cycle with 5 or 7 carbon atoms. The skilled person's scope for manoeuvre on this group's variation seems then more limited.

In summary, experimentation performed by the inventors with compounds of the current invention seem to demonstrate that the size of PDE4 catalytic site is large enough to accommodate several structural changes on the three binding sites disclosed previously. However, the most important handling margin seems anyway to be localized on the substituent R variation.

Galenic formulation of the invention compounds

The compounds of the invention are administrated as an appropriate composition accordingly to the nature and the scale of the disease to treat. The daily posology in humans is usually between 2 mg and 1 g of product that can be absorbed in one or several intakes. The compositions are prepared by usual methods for the skilled man and contain in a general manner 0.5 to 60 % by weight of active principle (formula I compounds) and 40 to 99.5 % by weight of appropriate pharmaceutical carrier.

The compositions of the current invention are then prepared under forms compatible with the desired administering route. As an example, the following pharmaceutical forms may be considered, although the listing provided below is not limiting:

Forms for administering by oral route :

Drinkable solutions, suspensions, powder sachets for drinkable solution, capsules, gastro-resistant capsules, prolonged-release forms, emulsions, HPMR capsules, lyophilisates to melt beneath the tongue.

1) Forms for administering by parenteral route :

Intravenous route :

Aqueous solutions, solutions water / co-solvent, solutions using one or several solubilizing agents, colloidal suspensions, emulsions, nano-particle suspensions usable for injection of long-lasting release forms, diffuse forms and liposomes.

Subcutaneous / intra-muscular route :

In addition, forms usable as intravenous route which are also usable for subcutaneous and intra-muscular routes, other form types such as suspensions, diffused forms, long-lasting release colloids as well as long-lasting release implants can also be used.

2) Forms for administering by topic route :

Among the most used topic forms, we distinguish creams, colloids (aqueous phases jellified by polymers), patches, which are dressings to stick directly on skin and which can be used to treat dermatitis without percutaneous penetration of the active substance, sprays, emulsions and solutions.

3) Forms for administering by pulmonary route :

In this category we distinguish forms of solutions for aerosols, powders for inhaling apparatus, and other appropriate forms.

4) Forms for administering by nasal route :

It concerns mainly here solutions for drops.

5) Forms for administering by rectal route :

We will note amongst others suppositories and colloids.

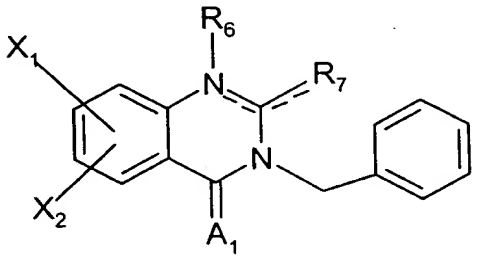
We can also consider the use of forms allowing ophthalmic solution administering or allowing administering of active principle by vaginal route.

Another important category of pharmaceutical form, which can be used in the context of the current invention, relates to forms allowing improvement in solubility of the active principle. As an example, we can consider the use of aqueous solutions of cyclodextrin, and more particularly forms including hydroxypropyl beta cyclodextrin. A detailed review of this type of pharmaceutical form is presented in an article issued in the *Journal of Pharmaceutical Sciences, 1142-1169, 85 (11), 1996*, and incorporated herein by.

Different pharmaceutical forms recommended above are disclosed in a detailed manner in the book « Pharmacie galénique » by A. LEHIR *(ed. Masson, 1992 (6th edition)* incorporated reference.

Intermediaries compounds

The current invention relates also to general formula III intermediaries compounds :



III

in which X_1, X_2, A_1, R_6 and R_7 are such as previously defined.

The invention relates particularly to general formula III intermediaries compounds in which :

X_1 and X_2 are such as previously defined, and
R_7 is bound to nitrogen in R_6 to form a triazol, substituted in position 1 by a Br, Cl, mercapto or lower thioalkyl group preferably CH_3-S-.

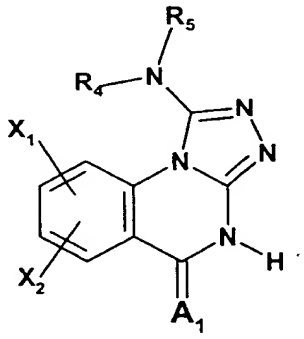
Among the groups defined above the following substituents are particularly preferred :
- In a general manner for the groups X_1, X_2, R_6 and R_7 :
- halogen : F, Cl, Br, I, preferably Br and Cl,

- lower alkyl : linear or branched comprising from 1 to 6, preferably from 1 to 3 carbon atoms ,
- lower alkoxy : linear or branched comprising from 1 to 5, preferably 1 to 3 carbon atoms ,
- lower thioalkyl : linear or branched comprising from 1 to 5, preferably 1 to 3 carbon atoms .

- In particular manner for the groups X_1 and X_2 :
X_1 and X_2 are particularly localized in position 6 and 7 of the main quinazolinone cycle.

- In particular manner for the groups R_6 and R_7 :
when R_7 is bound to the nitrogen in R_6 to form a cycle, the formed cycle is preferably a triazole, substituted in position 1 by a group Br, Cl, mercapto or lower thioalkyl, preferably CH_3-S-.

A second series of intermediaries includes the following general formula IV compounds:



IV

in which X_1, X_2, A_1, R_4 and R_5 are such as previously defined.

For the groups as above, the following substituents are particularly preferred :
- In a general manner for the groups X_1, X_2, R_4 and R_5 :
- halogen : F, Cl, Br, I, preferably Br and Cl,
- lower alkyl : linear or branched comprising from 1 to 6, preferably 1 to 3 carbon atoms ,
- lower alkyl : linear or branched comprising from 1 to 5, preferably 1 to 3 carbon atoms ,

- lower alkyl, R_4 and R_5 being able to be linked to form a saturated cycle or including one or several double-bonds including one or several heteroatoms chosen among O, S or N and possibly bridged by a lower alkyl, dialkylated gem or substituted by one or several groups chosen among hydroxy, keto, lower alkyl, lower alkoxy, phenyl alkyl or $CO\text{-}Q_1\text{-}Q_2\text{-}Q_3$, two atoms of the cycle then formed could also be part of another cycle chosen among phenyl or heteroaryl comprising from 4 to 8 atoms with 1 to 4 heteroatoms.

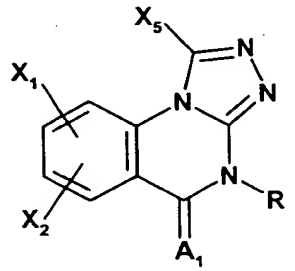
- In particular manner for the groups X_1 and X_2 :

X_1 and X_2 are particularly localized in position 6 and 7 of the main quinazolinone cycle.

- In particular manner for the groups R_4 and R_5 :

R_4 and R_5 are lower alkyl, R_4 and R_5 being able to be linked to form a saturated cycle or including one or several double-bonds with one or several heteroatoms chosen among O, S or N, substituted by one or several groups chosen among hydroxy, keto, lower alkyl or lower alkoxy. The particularly preferred substituents forming the group NR_4R_5 includes pyrrolidine, 3-hydroxy pyrrolidine, thiamorpholine, dimethyl amino, azepanyl and piperidinyl.

A third series of intermediaries includes the following general formula V compounds:



(V)

in which X_1, X_2, X_5, A_1 and R are such as previously defined.

For the groups as above, the following substituents are particularly preferred :

- In a general manner for the groups X_1, X_2 and X_5 :

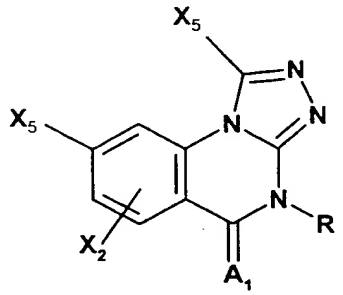
- halogen : F, Cl, Br, I, preferably Br and Cl,
- lower alkyl : linear or branched comprising from 1 to 6, preferably 1 to 3 carbon atoms,
- lower alkoxy : linear or branched comprising from 1 to 5, preferably 1 to 3 carbon atoms:

- In particular manner for the groups X_1 and X_2 :

X_1 and X_2 are particularly localized in position 6 and 7 of the main quinazolinone cycle.

- In particular manner for the group X_5 : X_5 is F, Br or Cl.

A fourth series of intermediaries includes the following general formula VI compounds :



(VI)

in which X_2, X_5, A_1 and R are such as previously defined.

For the groups as above, the following substituents are particularly preferred :

- In a general manner for the groups X_2 and X_5 :

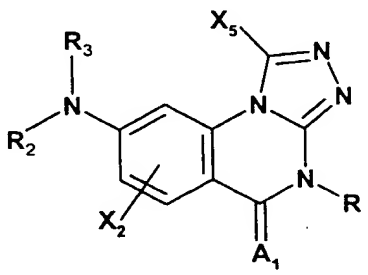
- halogen : F, Cl, Br, I, preferably Br and Cl,
- lower alkyl : linear or branched comprising from 1 to 6, preferably 1 to 3 carbon atoms ,
- lower alkoxy : linear or branched comprising from 1 to 5, preferably 1 to 3 carbon atoms .

- In particular manner for the group X_2 :

X_2 is particularly localized in position 7 of the main quinazolinone cycle.

- In particular manner for the group X_5 : X_5 is F, Br or Cl.

A fifth series of intermediaries includes the following general formula VII compounds :



in which X_2, X_5 A_1, R_2 R_3 are such as previously defined.

For the groups as above, the following substituents are particularly preferred :

- In a general manner for the groups X_2, X_5, R_2 and R_3 :

- halogen : F, Cl, Br, I, preferably Br and Cl,
- lower alkyl : linear or branched comprising from 1 to 6, preferably 1 to 3 carbon atoms ,
- lower alkoxy : linear or branched comprising from 1 to 5, preferably 1 to 3 carbon atoms ,
- hydrogen, lower alkyl, possibly substituted by one or several groups hydroxy, halogen, cyano, lower alkoxy or $-CO-Q_1-Q_2-Q_3$, R_2 and R_3 being able to be linked to form a cycle, including one or several heteroatoms chosen among O, S or N and possibly bridged by a lower alkyl, dialkylated gem or substituted by one or several groups chosen among hydroxy, keto, lower alkyl, lower alkoxy or $-CO-Q_1-Q_2-Q_3$.

- In particular manner for the group X_2 :

X_2 is particularly localized in position 7 of the main quinazolinone cycle.

- In particular manner for the group X_5 : X_5 is F, Br or Cl.

- In particular manner for the groups R_2 and R_3 :

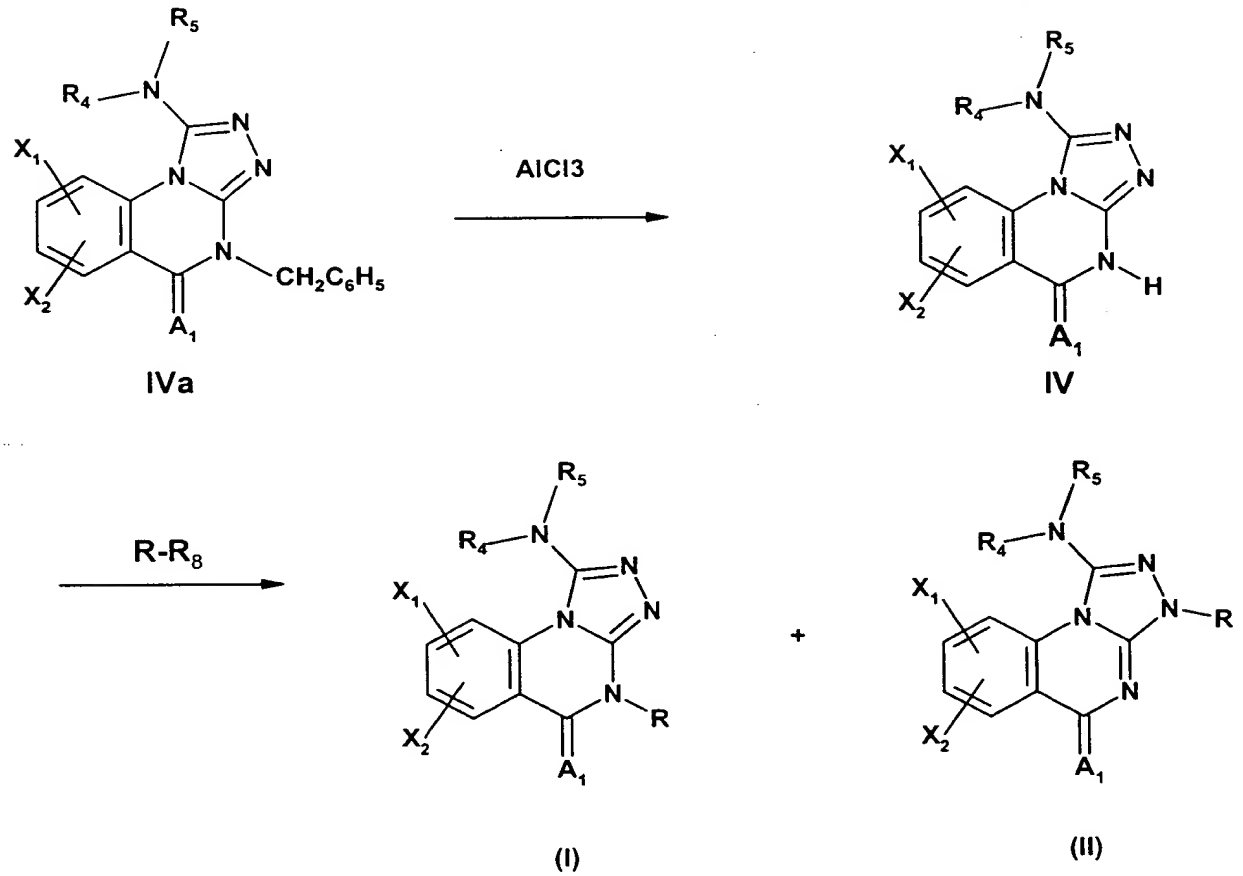
R_2 and R_3, similar or different, are hydrogen, lower alkyl R_2 and R_3 being able to be linked to form a cycle, including one or several heteroatoms chosen among O, S or N and possibly substituted by one or several groups chosen among hydroxy, keto, lower alkyl, lower alkoxy or $CO-Q_1-Q_2-Q_3$. Among the particular preferred embodiments of the substituent NR_2R_3, we find the groups azepanyl, pyrrolidine, NH_2 and $NHCH_3$.

Synthesis processes of formula I and II compounds

A) The compounds of the current invention can be obtained by bringing several synthesis processes into operation. Some of these synthesis processes are disclosed below.

The compounds of the current invention can be initially obtained in a convergent manner by the method represented in scheme 1.

SCHEME 1



IVa IV

(I) (II)

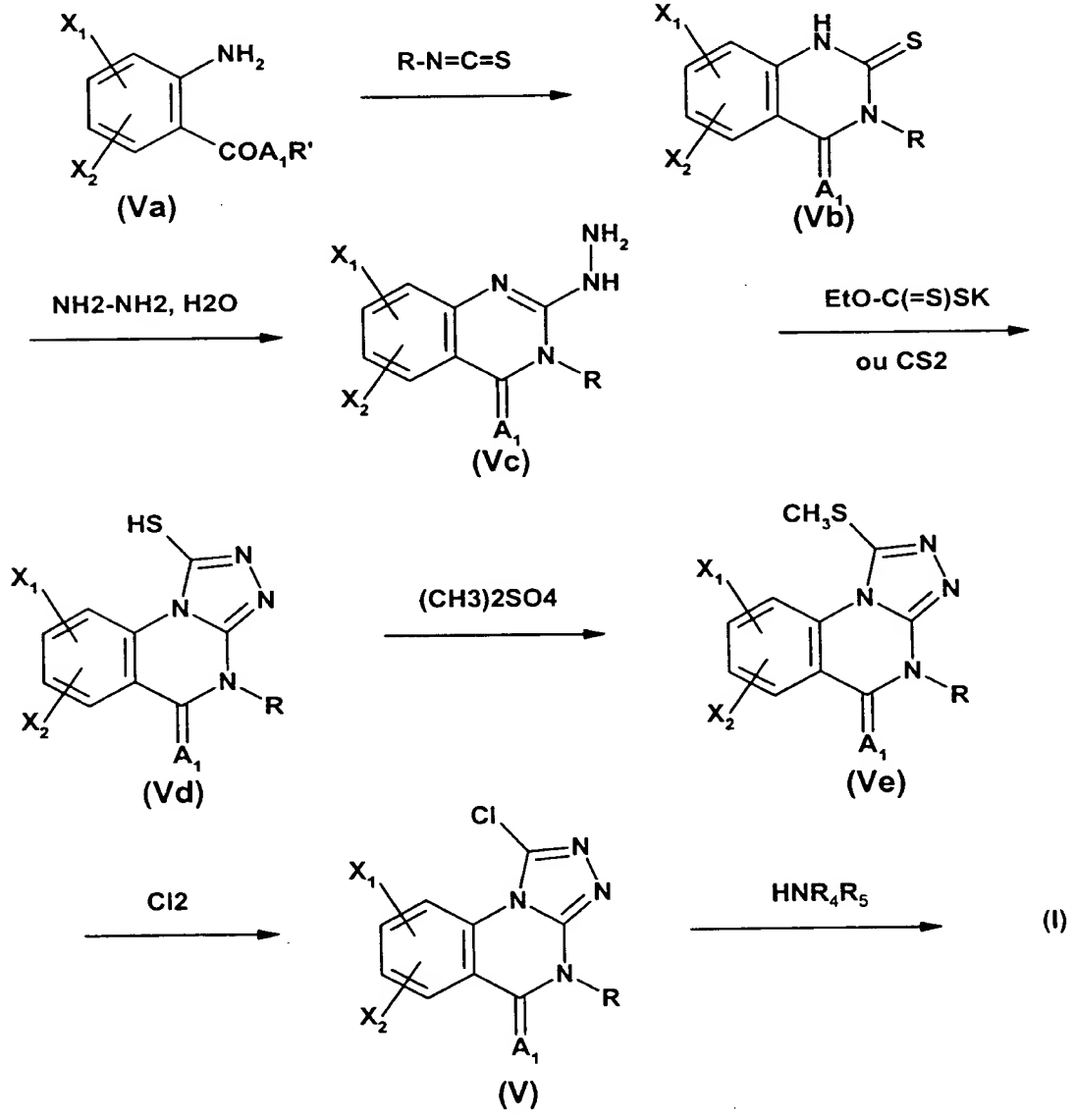
in which X_1, X_2, A_1, R, R_4 and R_5 are such as previously defined, and R_8 represents Cl, Br, OSO_2CH_3, OSO_2CF_3 or OSO_2Ar.

The 4-benzyl 1-amino triazolo [4,3-a] quinazoline-5-one and/ou –5-thione (IVa) is treated by aluminium trichloride in aromatic solvent such as benzene or toluene to make the corresponding compound N-debenzylated (IV). This one is therefore treated in basic conditions by a halide or a sulfonate chosen according to desired substituent R; for example sodium hydride in a solvent such as 1, 2-dimethoxyethane (DME) or cesium in dimethylformamide, to lead to 1-amino triazolo [4,3-a] quinazoline-5-ones of formula (I) and (II).

In fact, relying of the basic conditions used, the alkylation is a little regioselective in some cases. Then we obtain a mixture of N_4 and N_3, regioisomers, (I) and (II) respectively. The two compounds are usually separated by conventional chromatographic methods.

B) Another example of synthesis method used to construct correctly substituted formula (I) triazolo [4,3-a] quinazoline-5-one and/or –5-thione motif is illustrated by scheme 2 :

SCHEME 2



in which X_1, X_2, A_1, R, R_4 and R_5 are such as previously defined and,

R' represents a linear or branched lower alkyl group comprising from 1 to 6, preferably 1 to 3 carbon atoms.

An acid or anthranilic ester which is correctly substituted on the aromatic cycle (Va) is initially transformed into corresponding 2-thio quinazoline-4-one and/or –4-thione (Vb) by cyclization using isothiocyanate of alkyl, aryl or aralkyl, in a solvent such as acetic acid or pyridine.

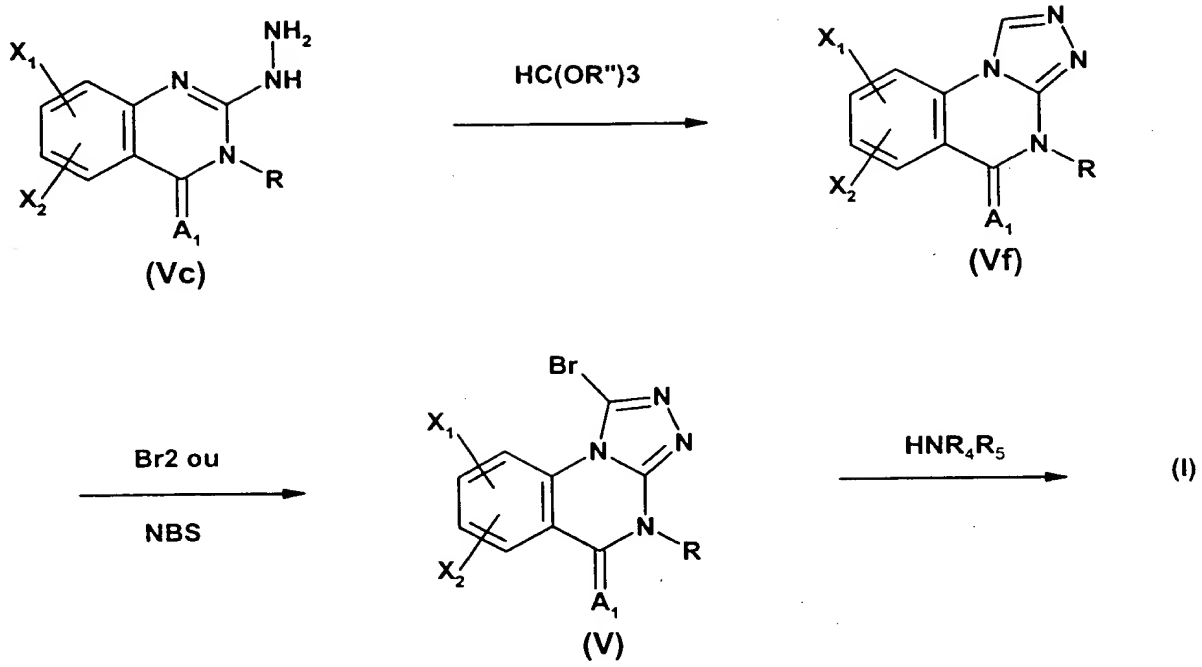
The thio quinazoline-4-one and/or –4-thione (Vb) is treated by hydrazine hydrate to give 2-hydrazino quinazoline-4-one and/or –4-thione (Vc) which is also cyclized into 1-mercapto triazolo [4,3-a] quinazoline-5-one and/or –5-thione (Vd) by action of potassium xanthogenate or other reagents such as CS_2.

By action of an alkylating agent such as dimethyl sulfate, the thiol (VI) is transformed into derivative 1-methylthio (Ve) which is then converted using chlorine, into 1-chloro triazolo [4,3-a] quinazoline-5-one and/ou –5-thione (V).

This latter is treated by a primary our secondary amine to lead finally to 1-amino triazolo [4,3-a] quinazoline-5-one of formula (I).

C) Another advantageous method in some cases is represented in scheme 3.

SCHEME 3



in which X_1, X_2, A_1, R, R_4 and R_5 are such as previously defined and,

R'' represents a linear or branched lower alkyl group comprising from 1 to 6, preferably 1 to 3 carbon atoms such as CH_3 or C_2H_5.

La 2-hydrazino quinazoline-4-one and/or –4-thione (Vc), obtained from an anthranilate in 2 steps (as illustrated in scheme 2), is cyclized using alkyl orthoformiate, in acid medium, into triazolo [4,3-a] quinazoline-5-one and/or –5-thione (Vf).

This is then brominated by bromine or N-bromosuccinimide (NBS) to give 1-bromotriazolo [4,3-a] quinazoline-5-one and/or –5-thione (V).

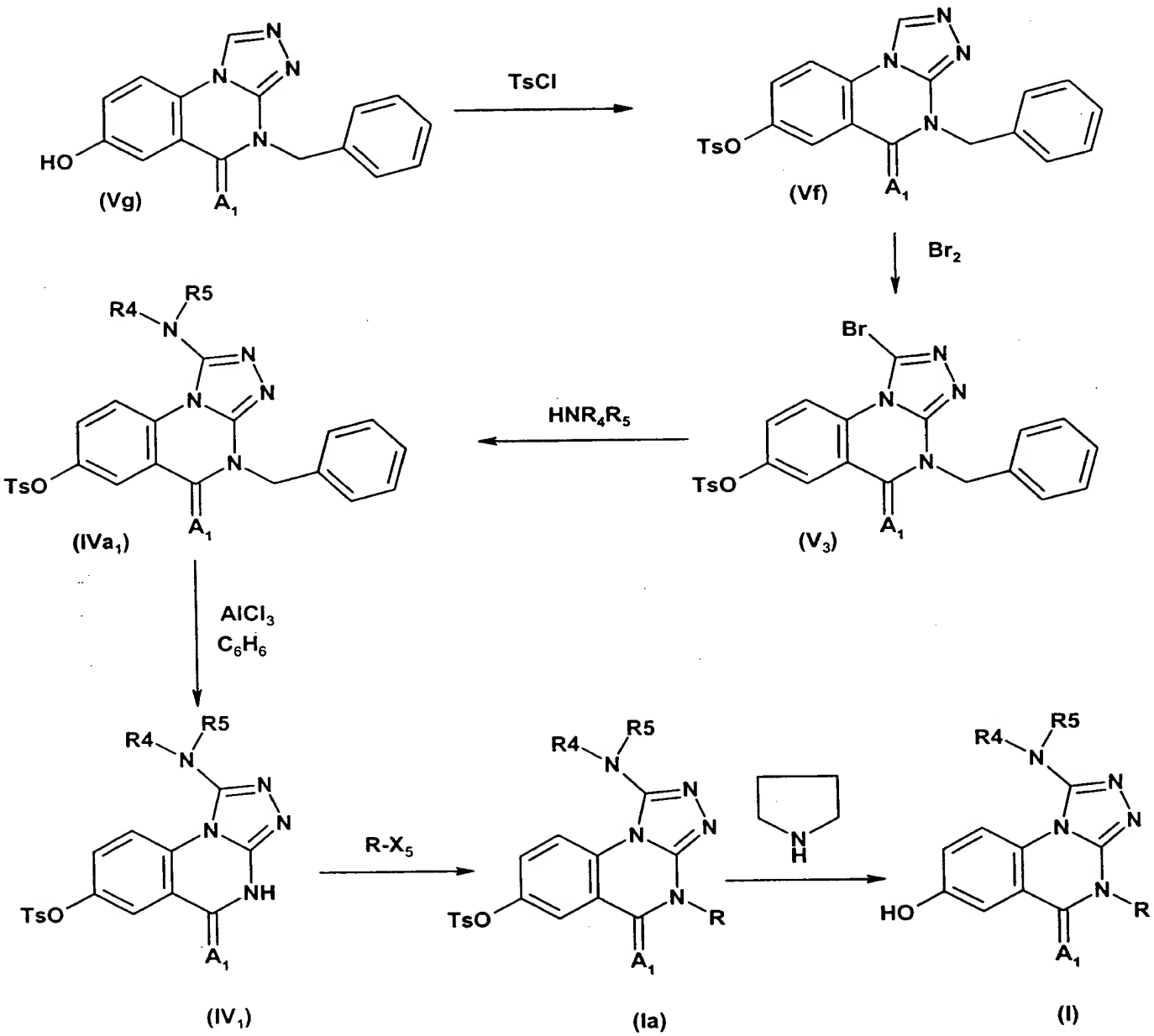
This brominated derivative is finally treated by ethanolic solution of primary or secondary amine to lead to formula (I) 1-amino triazolo [4,3-a] quinazoline-5-one and/or –5-thione.

D) When X_1 represents H and X_2 represent a reactive phenolic function OH, this group must generally be protected during the last steps of compound (I) synthesis. As an example, scheme 4 shows synthesis of such as hydroxyled in position 7 compound. The 4-benzyl-7-hydroxy-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one and/or –5-thione(Vg), obtained by a method represented in scheme 3, is treated by a compound allowing insertion of oxygen protector group (P) on the function OH. The person skilled in the art will be able to choose without any

problem the appropriate protector group. The protector group can be chosen also among silyl trimethyl, methoxymethyl, tolylsulfonyl, methylsulfonyl (mesyl) or also methoxyethylmethoxy (MEM). As an example, the compound (Vg) is treated by tosyl chloride, in a solvent such as methylene chloride, in the presence of a base or an amine such as triethylamine, to give the corresponding O-tosyled phenol (Vf). This is treated by bromine to lead to 4-benzyl-1-bromo-7-(4-tolylsulfonyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one and/or –5-thione (V_3), which reacts with an amine HNR4R5 by reflux, preferably in the presence of a base like sodium bicarbonate, in a solvent such as dimethylformamide, to give the 1-amino-4-benzyl-7-(4-tolylsulfonyl) –4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one and/or –5-thione (IVa_1).

We can then replace the benzyl group in position 4 by another group R, for example by debenzylating the compound (IVa_1) obtained previously using aluminium chloride in a solvent like benzene, then by alkylating the obtained intermediate (IV_1) by treatment with a halide or a sulfonate R-X_5, in basic conditions, to obtain the 1-amino-7-(4-tolylsulfonyl) –4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one and/or –5-thione (Ia) diversely substituted in position 4. These ones are preferably detosyled into 7-hydroxy derivative (I) for example by heating for several hours in pyrrolidine.

SCHEMA 4



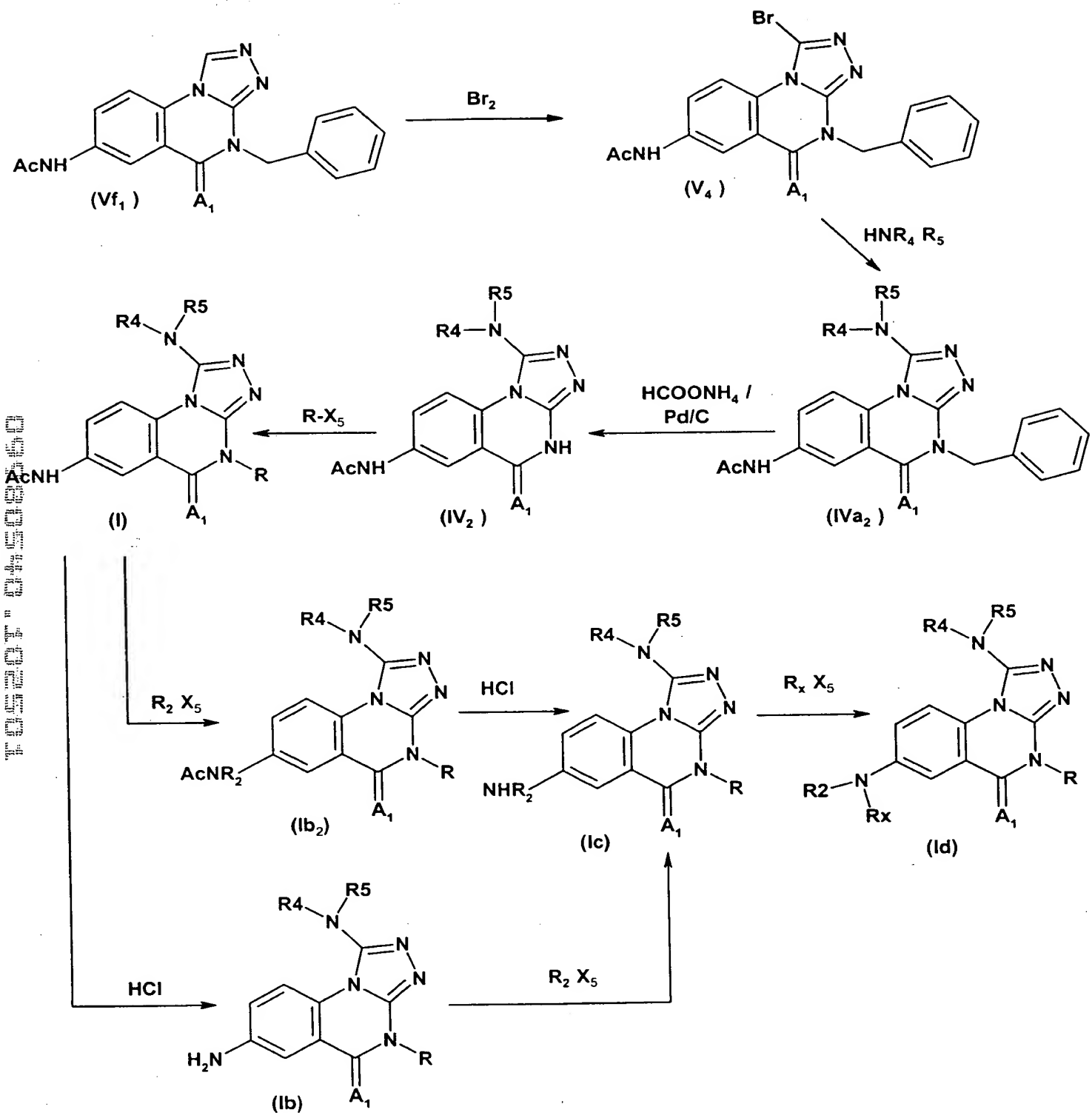
In which A_1, R_4 and R_5 are such as previously defined.

E) When X_1 represents H and X_2 represents a reactive anilino function NH2, NHR2 or NR_2R_x (R_2 such as previously defined and R_x represents R_2 or such as previously defined), the amino group NH_2 must generally be protected during the last steps of the compound (I) synthesis. As an example, scheme 5 shows synthesis of such as aminated compound in position 7. The 7-acetamido-4-benzyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one and/or –5-thione (Vf_1), obtained by a method represented in scheme 3, is treated by bromine to lead to

the 7-acétamido-4-benzyl-1-bromo-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one and/or –5-thione (V_4). This one is used in the reaction with an amine HNR_4R_5 by reflux, preferably in the presence of a base as sodium bicarbonate, in a solvent such as dimethylformamide, to give the 7-acétamido-1-amino-4-benzyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one and/or –5-thione (IVa_2). In the example disclosed above, the protector group (P_1) of the function NH is an acetyl group. However the man of art may choose another protector group, for example methylsulfonyl, tolylsulfonyl or phtalimido.

We can also replace the benzyl group in position 4 by another group R, for example by debenzylating the compound (IVa_2) obtained previously, using ammonium formiate and palladium on charcoal, in a solvent such as tetrahydrofuran, then by alkylating the obtained intermediate (IV_2) by treatment with a halide or a sulfonate $R\text{-}X_5$, in basic conditions, to obtain the 7-acetamido-1-amino-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one and/or –5-thione (I) diversely substituted in position 4. These ones can be N-deacetylated into final compounds (Ib) bearing a function NH2 in position 7, by classic methods like for example by reflux heating in an aqueous solution of hydrochloric acid. The compounds can be treated in at their turn, relying on the case, by a reagent $R_2\text{-}X_5$ (R_2 and X_5 having the meaning given previously) to lead to a final N-monosubstituted compound (Ic), which then can be treated by a reagent R_xX_5 to lead to a final N,N-disubstituted compound (1d). Also it is possible to treat 7-acetamido-1-amino-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one and/or –5-thione (I) diversely substituted in position 4 initially by a reagent R_2X_5 to obtain ($1b_2$) which is then N-deacetylated to obtain the compound (Ic).

SCHEMA 5

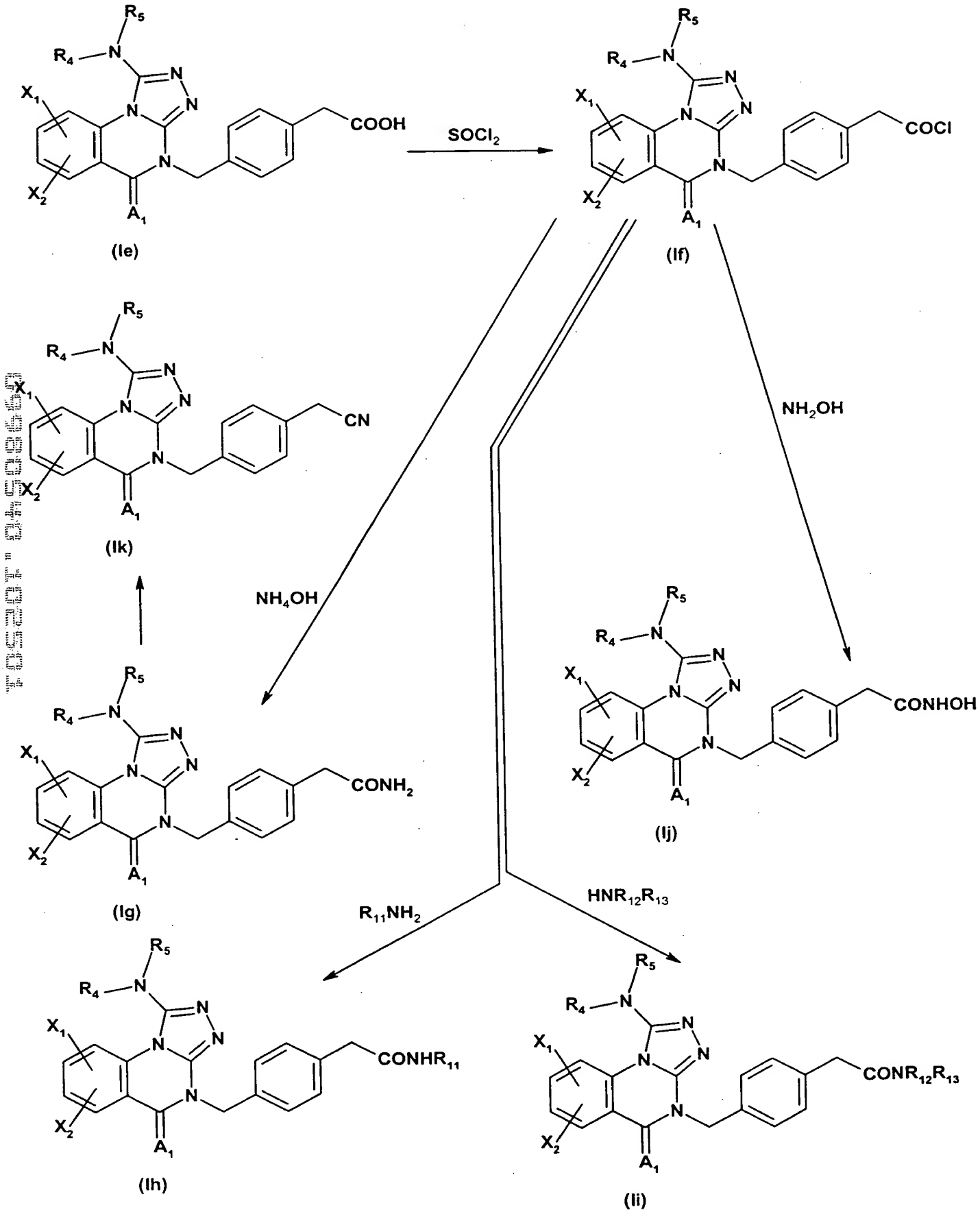


F) When the substituent R in position 4 of compounds (I) represents a group 4-(carboxymethyl)-benzyl, it can be advantageous to transform the carboxylic acid function into

ester, amide, nitrile or hydroxamic acid derived. For that, methods represented in scheme 6 can be applied to a general formula acid (Id). This is transformed into chloride of acid (Ie), which is directly condensed either with ammonia to give a primary amide (If), either with a primary or secondary amine to give a secondary (Ih) or tertiary (Ii) amide respectively. (In these structures, R_{11} has the same meaning as R_2 and R_{12} have the same meaning as R_4, R_5 respectively).

The hydroxamic acid (Ij) can be obtained by reaction of chloride of acid (Ie) with hydroxylamine. The primary amide (If) can be dehydrated by classic and current methods, for example using phosphorus pentoxide to lead to corresponding nitrile (Ig).

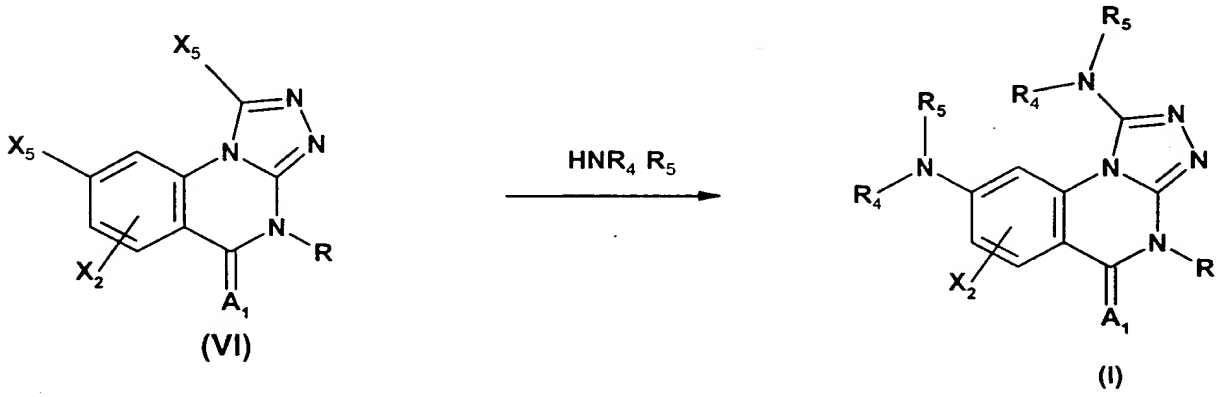
SCHEMA 6


R5
R4
N
X1
X2
A1
COOH
(Ie)
SOCl2
COCl
(If)
NH2OH
CN
(Ik)
NH4OH
CONH2
(Ig)
CONHOH
(Ij)
R11NH2
HNR12R13
CONHR11
(Ih)
CONR12R13
(Ii)

In which X_1, X_2, A_1, R_4 and R_5 are such as previously defined.

G) The compounds of structure (I) in which X_1 or X_2 represents an amino NR_2R_3 group in position 8 identical to the NR_4R_5 group, can also be obtained by heating of corresponding 1-bromo (VI ; X_5 = hal) intermediates in the presence of an excess of HNR_4R_5 amine, without solvent or in a solvent such as dimethylformamide as illustrated in scheme 7.

SCHEME 7

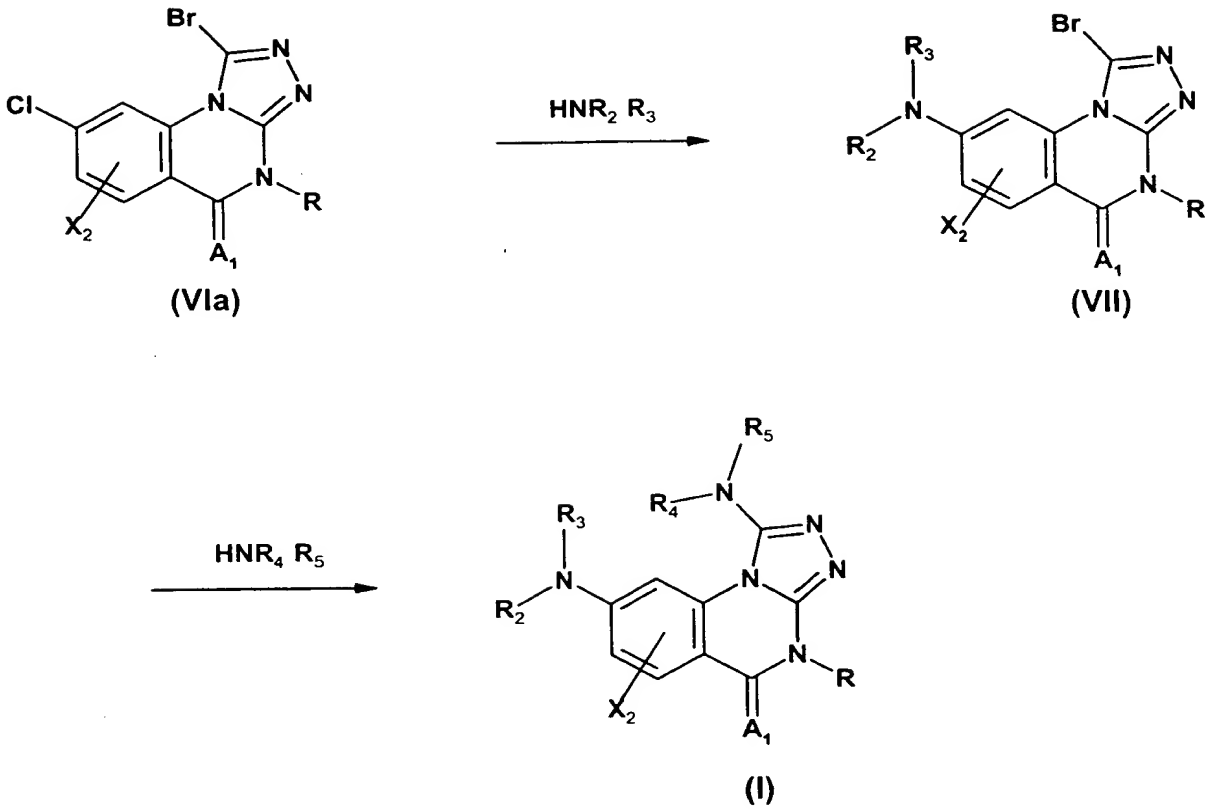


in X_2, X_5, A_1, R, R_4 and R_5 are such as previously defined.

However it is preferable to avoid for this reaction type substituents R including a halogen group able to react in a competitive manner with the reagent HNR_4R_5.

H) In the case where two NR_2R_3 and NR_4R_5 amino groups are different, a slightly modified synthesis path is indicated in scheme 8.

SCHEME 8



in which X_2, A_1, R, R_2, R_3, R_4 and R_5 are such as previously defined. The substituent amino NR_2R_3 is localized in position 8.

1-bromo 8-chlorotriazolo [4,3-a] quinazoline-5-one and/or –5-thione (VIa) correctly substituted in position 4, and prepared as previously by bromination of non-substituted in position 1 derivative, is treated by slight excess of amine HNR_2R_3, in a solvent such as dimethylformamide to lead to intermediate (VII).

This intermediate is also heated in an excess of amine HNR_4R_5, in a solvent such as dimethylformamide to lead to compound (I).

Surprisingly, the inventors have noticed that reactivity of the halogen atom in position 8 is much more important than reactivity of the other halogen atom of the intermediate. This allows then a first selective reaction on the level of this halogen in position 8 than can be followed by reaction on the level of the second halogen. The example as above illustrates use of chlorine in position 8. However it is possible to use other halogens such as bromine and fluorine, the latter proving to be particularly reactive.

Examples

A. Type (I) and (II) compounds

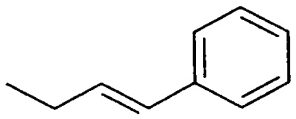
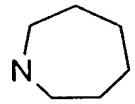
Examples 1 and 2

METHOD A : 1-Azepanyl-7-chloro-4-(3-phénylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (ex. 1)

(I): $X_1 = 7 - Cl$; $X_2 = H$;

1-Azepanyl-7-chloro-3-(3-phénylallyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (ex. 2)

(II) : $X_1 = 7 - Cl$; $X_2 = H$;

R=  ; NR_4R_5=  et

In a reactor protected from humidity, we place 2.5 g (7.87 mmol) of 1-Azepan-yl-7-chloro-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one, in suspension in 35 ml of 1,2-dimethoxyethane then we shake.

Under inert atmosphere, we then add 240 mg of sodium hydride suspension at 75 % (representing 7.90 mmol NaH).

The mixture is heated to 60° C under shaking for 6 hours.

Then we add 1.56 g (7.90 mmol) of cinnamyl bromide by fraction.

The obtained mixture is heated then to 60° C for 20 hours, under shaking.

After cooling down, the suspension is poured into 200 ml of iced water.

We extract three times with ethyl acetate; the joined organic phases are washed with aqueous solution saturated with sodium chloride, dried on sodium sulfate; then the solvent is evaporated under vacuum.

We obtain 3.5 g of crude mixture of the two regioisomers (theory : 3.4 g).

The 2 isomers are separated by flash chromatography on silica column with elution using methylene chloride 99 / methanol 1 mixture.

In order of elution we obtain,:

1) 0.58 g of compound from example 1

Yield = 17 %

F (Tottoli) = 125°C

CCM (CH_2 Cl_2 98 / CH_3 OH 2) = 0.60

RMN[1] H δ (ppm) $CDCl_3$: 1.7 – 2.0 (m, 8H) ; 3.3 – 3.5 (m, 4H) ; 5.05 (d, 2H) ; 6.45 (dt, 1H) ; 6.9

(d, 1H) ; 7.15 – 7.3 (m, 3H) ; 7.35 (d, 2H) ; 7.75 (d, 1H) ; 8.35 (s, 1H) ; 8.4 (d, 1H).

2) 2.1 g of compound from example 2

Yield = 61.5 %

F (Tottoli) = 188°C

CCM (CH_2 Cl_2 98 / CH_3 OH 2) : Rf = 0.35.

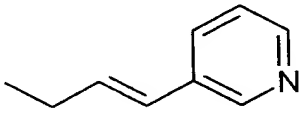
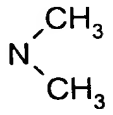
RMN ^{1}H δ (ppm) $CDCl_3$:

1.7 – 2.0 (m, 8H) ; 3.4 (m, 4H) ; 4.9 (d, 2H) ; 6.35 (d, 1H) ; 6.75 (d, 1H) ; 7.2 – 7.45 (m, 5H) ; 7.65 (d, 1H) ; 8.2 (d, 1H) ; 8.45 (s, 1H)

Example 3 :

METHOD B : 7-bromo-1-(N,N-dimethylamino)-4-[3-(3-pyridyl)-allyl]-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (ex. 3)

(I): X_1 = 7 – Br ; X_2 = H ;

R=  ; NR4R5= 

In a reactor equipped with magnetic shaker and refrigeration, we resuspend 7.4 g (0.024 mol) of 7-bromo-1-(N,N-dimethylamino)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one in 200 ml de 1,2-dimethoxyethane then we shake. We add 17.0g (0.052mol) of cesium carbonate then shake at ambient temperature for 15 minutes. 4.5g (0.024mol) of 3-(3-pyridyl)-allyl chloride hydrochloride are then added by fraction, then the mixture is heated to 70°C, under shaking, for 3 hours. The solvent is evaporated under vacuum then the residue is then put in suspension in 300 ml of iced water. After repeated extractions with ethyl acetate, the joined organic phases are washed with aqueous solution saturated with sodium chloride, dried on sodium sulfate then the solvent is evaporated under vacuum.

The residue is chromatographied on silica column by elution using CH_2Cl_2 98 / CH_3OH 2 / NH_4OH 0,2 mixture. We recover 6.3g of isomer (I) pure **in CCM**. This one is recrystallized in 20ml of isopropanol to give 5.3g of example 3 compound:

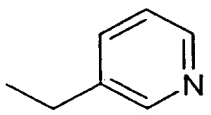
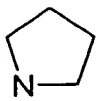
Yield = 52%

RMN^1 H δ (ppm) $CDCl_3$: 2.95 (s, 6H) ; 5.1 (d, 2H) ; 6.45 (dt, 1H) ; 6.8 (d, 1H) ; 7.15 (m, 1H) ; 7.65 (d, 1H) ; 7.9 (d, 1H) ; 8.25 (d, 1H) ; 8.4 – 8.6 (m, 3H).

Examples 4 and 5 :

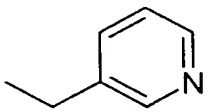
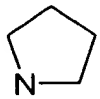
METHOD C : 7-bromo-1-(pyrrolidin-1-yl)-4-[(3-pyridyl)-methyl]-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (ex. 4)

(I): X_1 = 7 – Br ; X_2 = H ;

R=  ; NR4R5= 

7-bromo-1-(pyrrolidin-1-yl)-3-[(3-pyridyl)-methyl]-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (ex. 5)

(II) : X1 = 7-Br ; X2 = H ;

R=  ; NR4R5= 

In a reactor protected from humidity, equipped with magnetic shaking and refrigeration, we add 2.0g (0.006 mol) of 1-(pyrrolidin-1-yl)-7-bromo-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one into 125 ml of dimethylsulfoxyde (DMSO) solution then we add 1.0g (0.018 mol) of finely crushed potash. The mixture is shaken at ambient temperature for 1.5 h, until obtaining of slightly cloudy solution. Then we add once 0.82g (0.005 mol) of 3-picolyl chloride hydrochloride then keep shaking at ambient temperature for 4 hours.

The obtained mixture is poured into iced water and the resulting suspension is extracted 3 times with ethyl acetate. The joined organic extracts are washed in NaCl saturated solution, dried on Na_2SO_4 then concentrated under vacuum. We obtain 2.0g of crude mixture of the 2 regioisomers which are separated by chromatography on silica column by elution using CH_2Cl_2 98 - CH_3OH 2 - NH_4OH 0.4 mixture.

In elution order we obtain:

1) 1.2g of majority product which is recrystallized in methanol to give after drying under vacuum 1,1g of example 4 compound.

Yield = 57 %

F (Tottoli) = 206-207°C

CCM (CH_2Cl_2 97 / CH_3OH 3 / NH4OH 0.3) : Rf = 0.30

RMN^1 H δ (ppm) $CDCl_3$: 1.95 – 2.1 (m, 4H) ; 3.35 – 3.45 (m, 4H) ; 5.45 (s, 2H) ; 7.2 – 7.3 (dd, 1H) ; 7.85 (d, 1H) ; 8.0 (d, 1H) ; 8.2 (d, 1H) ; 8.45 – 8.55 (m, 2H) ; 8.9 (s, 1H).

2) 0.25g of minority product which is recrystallized in methanol to give after drying under vacuum 0.17g of example 5 compound .

Yield = 12%

F (Tottoli) = 261-262°C

CCM (CH_2Cl_2 97 / CH_3OH 3 / NH4OH 0.3) : Rf = 0.20

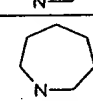
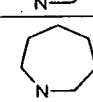
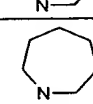
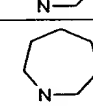
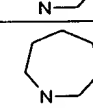
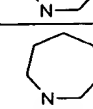
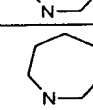
RMN^1 H δ (ppm) $CDCl_3$: 1.9 – 2.05 (m, 4H) ; 3.2 – 3.4 (m, 4H) ; 5.25 (s, 2H) ; 7.1 – 7.2 (m, 1H) ; 7.7 (d, 1H) ; 7.8 (d, 1H) ; 7.9 (d, 1H) ; 8.45 – 8.60 (m, 2H) ; 8.65 (s, 1H).

Compounds (I) of examples 6 to 108 and compounds (II) of examples 109 to 162, in which $X_2 = H_1$ are prepared according to process of example 1 :

Compounds (I) : Table 1

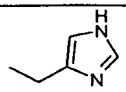
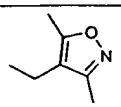
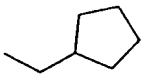
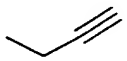
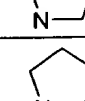
Compounds (II) : Table 2

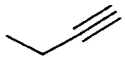
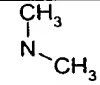
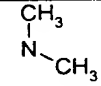
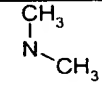
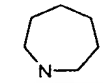
TABLE 1

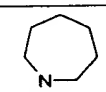
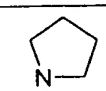
N°. Compound	X1	R	NR4R5	Yield (%)	MP (°C)	Method
6	H	(E) C6H5CH=CHCH2		11	144	A
7	7-Cl	CH2=CHCH2		9	-	A
8	7-Cl	4-CH3C6H4CH2		16	163	A
9	7-Cl	2-ClC6H4CH2		6	160-162	A
10	7-Cl	3-ClC6H4CH2		35	157	A
11	7-Cl	4-ClC6H4CH2		20	166	A
12	7-Cl	4-BrC6H4CH2		25	104-110	A
13	7-Cl	4-FC6H4CH2		48	150	A
14	7-Cl	4-CF3C6H4CH2		22	138	A
15	7-Cl	4-CNC6H4CH2		49	165-168	A
16	7-Cl	2-(CH3O)C6H4CH2		6	98-100	A
17	7-Cl	3-(CH3O)C6H4CH2		22	138	A
18	7-Cl	4-(CH3O)C6H4CH2		26	138	A
19	7-Cl	3,4-Cl2C6H3CH2		19	-	A
20	7-Cl	3,4-(CH3O)2C6H3CH2		41	172	A
21	7-Cl	(2-pyridyl)CH2		16	152	A
22	7-Cl	(3-pyridyl)CH2		29	155	A

N.. Compound	X1	R	NR4R5	Yield (%)	MP (°C)	Method
23	7-Cl	(4-pyridyl)CH2		64	137	A
24	7-Cl	C6H5CH2CH2		5	105	A
25	7-Cl	4-(CH3O)C6H4(CH2)2		12	136	A
26	7-Cl	C6H5(CH2)3		17	-	A
27	7-Cl	C6H5C(=O)CH2		26,5	105-107	A
28	7-Cl	4-(CH3O)C6H4C(=O)CH2		30	191	A
29	7-Cl	4-ClC6H4C(=O)CH2		36	190	A
30	7-Cl	4-(CH3O)-3-(COOCH3)-C6H3C(=O)CH2		18	140	A
31	7-Cl	(3-pyridyl)-CH2		39	176	C
32	7-Br	4-ClC6H4CH2		8	179	A
33	7-Br	4-FC6H4CH2		21	158	A
34	7-Br	4-CNC6H4CH2		21	190	A
35	7-Br	3,4-(CH3O)2C6H3CH2		23,5	185	A
36	7-Br	(3-pyridyl)-CH2		4	180	C
37	7-Br	(E) C6H5CH=CHCH2		64	155	B
38	7-Br	(E) 4-Cl-C6H4CH=CHCH2		25	176	B
39	7-Br	(E) 4-(CH30)C6H4CH=CHCH2		30	129	B
40	7-Br	(E) (3-pyridyl)CH=CHCH2		12	185	B

N.. Compound	X1	R	NR4R5	Yield (%)	MP (°C)	Meth d
41	7-Br	(E) (4-pyridyl)CH=CHCH2		39	216	B
42	7-Br	4-CH3C6H4CH2		53	215	B
43	7-Br	4-ClC6H4CH2		12	105	A
44	7-Br	4-FC6H4CH2		42	166	A
45	7-Br	3-CNC6H4CH2		52	206	B
46	7-Br	4-CNC6H4CH2		19	116	A
47	7-Br	4-(COOCH3)C6H4CH2		54	205	A
48	7-Br	4-NO2C6H4CH2		52	200	B
49	7-Br	4-(CH3O)C6H4CH2		39	169	B
50	7-Br	4-(OCOCH3)C6H4CH2		21	195	B
51	7-Br	4-OHC6H4CH2		13	288	B
52	7-Br	3,4-(CH3O)2C6H3CH2		15	151	A
53	7-Br	3,4-(OCH2O)C6H3CH2		21	194	A
54	7-Br	3,5-(CH3O)2C6H3CH2		31	-	A
55	7-Br	3,4,5-(CH3O)3C6H2CH2		35	141-143	A
56	7-Br	4-(CH2COOH)C6H4CH2		17	260	B
57	7-Br	(E) C6H5CH=CHCH2		57	152-155	A
58	7-Br	(Z) C6H5CH=CHCH2		24	110	B

N.. Compound	X1	R	NR4R5	Yield (%)	MP (°C)	Method
59.	7-Br	(E) (4-ClC6H4)-CH=CHCH2		45	187	B
60	7-Br	(E) (4-CH3O)C6H4CH=CHCH2		32	171	B
61	7-Br	(E) (3-pyridyl)-CH=CHCH2		10	102	B
62	7-Br	(E) (4-pyridyl)-CH=CHCH2		38	167	B
63	7-Br			4	290(dec)	B
64	7-Br			60	221	B
65	7-Br			32	155	B
66	7-Br	n-butyl		39	135	B
67	7-Br	CH2CF3		14	202	B
68	7-Br	CH2CH2OH		25	240	B
69	7-Br	CH2CH2N(C2H5)2		50	215 (HCl)	C
70	7-Br			36	204	B
71	7-Br	CH2CH2OC6H5		25	171	B
72	7-Br	CH2CH2SC6H5		20	122	B
73	7-Br	CH(C6H5)COOCH3		14	184	B
74	7-Br	4-CNC6H4CH2		72	200	B
75	7-Br	3,4-(CH3O)2C6H3CH2		67	178	B
76	7-Br	(E) C6H5CH=CHCH2		8	-	A

N. Compound	X1	R	NR4R5	Yield (%)	MP (°C)	Method
77	7-Br	(E) (3-pyridyl)CH=CHCH2		48	177	B
78	7-Br	4-CH3C6H4CH2		56	223	B
79	7-Br	4-CNC6H4CH2		56	207	B
80	7-Br	4-OHC6H4CH2		15	284	B
81	7-Br	4-(COOCH3)C6H4CH2		35	197	B
82	7-Br	4-(CH2COOH)C6H4CH2		8	246	B
83	7-Br	4-(CH2CN)C6H4CH2		<1	230	B
84	7-Br	(3-pyridyl)-CH2		28	142	B
85	7-Br	(E) C6H5CH=CHCH2		63	171	B
86	7-Br	(Z) C6H5CH=CHCH2		28	167	B
87	7-Br	(E) (4-pyridyl)-CH=CHCH2		48	115	B
88	7-Br			<1	234	B
89	7-Br	C6H5C≡CCH2		15	159	B
90	7-Br	CH(C6H5)COOCH3		18	243	B
91	7-CH3	(3-pyridyl)-CH2		64	175	C
92	7-CH3	(E) C6H5CH=CHCH2		16	195	A
93	7-CH3	4-CNC6H4CH2		84	166	B
94	7-CH3	3,4-(CH3O)2C6H3CH2		52	184	B

N°. Compound	X1	R	NR4R5	Yield (%)	MP (°C)	Method
95	7-CH3	4-(COOCH3)C6H4CH2		44	230	B
96	7-CH3	4-(CH2COOH)C6H4CH2		21	262	B
97	7-CH3	(3-pyridyl)-CH2		10	139	C
98	7-CH3	(E) C6H5CH=CHCH2		17	173	A
99	7-CH3	4-(CH2COOH)C6H4CH2		10	-	B
100	7-CH3	(E) (3-pyridyl)CH=CHCH2		51	230	B
101	7-CH3	4-CNC6H4CH2		73	201	B
102	7-CH3	4-(CH2COOH)C6H4CH2		3	-	B
103	7-CH3	(E) C6H5CH=CHCH2		50	171	B
104	7-CH3	(E) (3-pyridyl)CH=CHCH2		53	155	B
105	7-CH3	(E) (4-pyridyl)-CH=CHCH2		66	119	B
106	8-CH3	(E) C6H5CH=CHCH2		52	-	A
107	7-CN	4-CNC6H4CH2		43	147-149	B
108	7-OH	(E) C6H5CH=CHCH2		3	295(dec)	A

- <u>Compound 6</u> :

R.M.N.^{1}H δ (ppm) : 1.7 – 1.85 (m, 8H) ; 3.3 – 3.4 (m, 4H) ; 4.95 (d, 2H) ; 6.4 – 6.5 (dt, 1H) ; 6.7 – 6.75 (d, 1H) ; 7.25 (t, 1H) ; 7.3 (t, 2H) ; 7.45 (d, 2H) ; 7.6 (t, 1H) ; 7.95 (t, 1H) ; 8.25 (d, 1H) ; 8.4 (d, 1H)

Solvent : DMSO

- **Compound 7** :

R.M.N.^{1}H δ (ppm) : 1.5 – 1.9 (m, 8H) ; 3.3 (m, 4H) ; 4.8 (d, 2H) ; 5.2 (d, 1H) ; 5.4 (d, 1H) ; 5.95 (m, 1H) ; 7.65 (d, 1H) ; 8.25 (s, 1H) ; 8.3 (d, 1H)

Solvent : $CDCl_3$

- **Compound 8** :

R.M.N.^{1}H δ (ppm): 1.7 – 2.0 (m, 8H) ; 2.3 (s, 3H) ; 3.35 (m, 4H) ; 5.4 (s, 2H) ; 7.1 (d, 2H) ; 7.6 (d, 2H) ; 7.7 (d, 1H) ; 8.35 (m, 2H)

Solvent : $CDCl_3$

- **Compound 9** :

R.M.N.^{1}H δ (ppm) : 1.75 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 5.6 (s, 2H) ; 7.05 – 7.25 (m, 3H) ; 7.4 (d, 1H) ; 7.75 (d, 1H) ; 8.35 (s, 1H) ; 8.45 (d, 1H)

Solvent : $CDCl_3$

- **Compound 10** :

R.M.N.^{1}H δ (ppm) : 1.6 – 2.0 (m, 8H) ; 3.35 (m, 4H) ; 5.4 (s, 2H) ; 7.2 (m, 2H) ; 7.55 (s, 1H) ; 7.65 (s, 1H) ; 7.7 (d, 1H) ; 8.35 (m, 2H)

Solvent : $CDCl_3$

- **Compound 11** :

R.M.N.^{1}H δ (ppm) : 1.65 – 1.9 (m, 8H) ; 3.3 (m, 4H) ; 5.35 (s, 2H) ; 7.2 (d, 2H) ; 7.55 (d, 2H) ; 7.65 (d, 1H) ; 8.25 (m, 2H)

Solvent : $CDCl_3$

- **Compound 12** :

R.M.N.^{1}H δ (ppm) : 1,7 – 2 (m, 8H) ; 3,4 (m, 4H) ; 5,4 (s, 2H) ; 7,4 (d, 2H) ; 7,55 (d, 2H) ; 7,7 (d, 1H) ; 8,3 (s, 1H) ; 8,35 (d, 1H)

Solvent : $CDCl_3$

- **Compound 13** :

R.M.N.^{1}H δ (ppm) : 1.75 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 5.4 (s, 2H) ; 7.0 (m, 2H) ; 7.7 (m, 3H) ; 8.35 (m, 2H)

Solvent : $CDCl_3$

- **Compound 14** :

R.M.N.^{1}H δ (ppm) : 1.7 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 5.5 (s, 2H) ; 7.55 (d, 2H) ; 7.7 (d, 1H) ; 7.8 (d, 2H) ; 8.3 – 8.45 (m, 2H)

Solvent : $CDCl_3$

- **Compound 15** :

R.M.N.^{1}H δ (ppm) : 1.65 – 2 (m, 8H) ; 3.4 (m, 4H) ; 5.45 (s, 2H) ; 7.55 (d, 2H) ; 7.7 – 7.85 (m, 3H) ; 8.25 – 8.45 (m, 2H)

Solvent : $CDCl_3$

- **Compound 16** :

R.M.N.^{1}H δ (ppm) : 1.75 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 3.9 (s, 3H) ; 5.5 (s, 2H) ; 6.8 (t, 1H) ; 6.9 (d, 1H) ; 7.1 (d, 1H) ; 7.2 (t, 1H) ; 8.35 (s, 1H) ; 8.4 (d, 1H)

Solvent : $CDCl_3$

- **Compound 17** :

R.M.N.^{1}H δ (ppm) : 1.75 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 3.8 (s, 3H) ; 5.5 (s, 2H) ; 6.8 (m, 1H) ; 7.25 (m, 3H) ; 7.75 (d, 1H) ; 8.4 (m, 2H)

Solvent : $CDCl_3$

- **Compound 18** :

R.M.N.^{1}H δ (ppm) : 1.75 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 3.75 (s, 3H) ; 5.4 (s, 2H) ; 6.85 (d, 2H) ; 7.7 (m, 3H) ; 8.35 (m, 2H)

Solvent : $CDCl_3$

- **Compound 19** :

R.M.N.^{1}H δ (ppm) : 1.7 – 2.0 (m, 8H) ; 3.35 (m, 4H) ; 5.4 (s, 2H) ; 7.3 (d, 1H) ; 7.5 (d, 1H) ; 7.75 (m, 2H) ; 8.3 (s, 1H) ; 8.35 (d, 1H)

Solvent : $CDCl_3$

- **Compound 20** :

R.M.N.^{1}H δ (ppm) : 1.75 – 1,95 (m, 8H) ; 3.4 (m, 4H) ; 3.85 (s, 3H) ; 3.90 (s, 3H) ; 5.4 (s, 2H) ; 6.75 (d, 1H) ; 7.35 (m,2H) ; 7.7 (d, 1H) ; 8.35 (m, 2H)

Solvent : $CDCl_3$

- **Compound 21** :

R.M.N.^{1}H δ (ppm) : 1.7 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 5.6 (s, 2H) ; 7.15 (m, 1H) ; 7.4 (d, 1H) ; 7.6 (m, 1H) ; 7.75 (d, 1H) ; 8.35 (s, 1H) ; 8.4 (d, 1H) ; 8.45 (m, 1H)

Solvent : $CDCl_3$

- **Compound 22** :

R.M.N.^{1}H δ (ppm) : 1.6 – 1.95 (m, 8H) ; 3.35 (m, 4H) ; 5.4 (s, 2H) ; 7.2 (m, 1H) ; 7.7 (d, 1H) ; 8.0 (m, 1H) ; 8.3 (m, 2H) ; 8.5 (m, 1H) ; 8.9 (s, 1H)

Solvent : $CDCl_3$

- **Compound 23** :

R.M.N.^{1}H δ (ppm) : 1.6 – 1.9 (m, 8H) ; 3.3 (m, 4H) ; 5.35 (s, 2H) ; 7.4 (d, 2H) ; 7.65 (d, 1H) ; 8.25 (s, 1H) ; 8.3 (d, 1H) ; 8.45 (d, 2H)

Solvent : $CDCl_3$

- **Compound 24** :

R.M.N.^{1}H δ (ppm) : 1.7 – 2.1 (m, 8H) ; 3.15 (t, 2H) ; 3.4 (m, 4H) ; 4.5 (t, 2H) ; 7.2-7.45 (m, 5H) ; 7.7 (d, 1H) ; 8.35 (s, 1H) ; 8.35 (s, 1H) ; 8.4 (d, 1H)

Solvent : $CDCl_3$

- **Compound 25** :

R.M.N.^{1}H δ (ppm) : 1.7 – 1.95 (m, 8H) ; 3.05 (t, 2H) ; 3.4 (m, 4H) ; 3.8 (s, 3H) ; 4.45 (t, 2H) ; 6.85 (d, 2H) ; 7.25 (d, 2H) ; 7.7 (d, 1H) ; 8.3 (s, 1H) ; 8.4 (d, 1H)

Solvent : $CDCl_3$

- **Compound 26** :

R.M.N.^{1}H δ (ppm) : 1.7 – 2.0 (m, 8H) ; 2.2 (qn, 2H) ; 2.75 (t, 2H) ; 3.35 (m, 4H) ; 4.35 (t, 2H) ; 7.0 – 7.2 (m, 5H) ; 7.7 (d, 1H) ; 8.3 (s, 1H) ; 8.35 (d, 1 H)

Solvent : $CDCl_3$

- **Compound 27** :

R.M.N.1H δ (ppm) : 1.65-1.85(m,8H) ; 3.35(m,4H) ; 5.7(s,2H) ; 7.6(t,2H) ; 7.75(t,1H) ; 8.05(d,1H) ; 8.15(m,3H) ; 8.4(d,1H)

Solvent : DMSO

- **Compound 28** :

R.M.N.^{1}H δ (ppm) : 1.75 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 3.9 (s, 3H) ; 5.7 (s, 2H) ; 7.0 (d, 2H) ; 7.8 (d, 1H) ; 8.05 (d, 2H) ; 8.35 (s, 1H) ; 8.45 (d, 1 H)

Solvent : $CDCl_3$

- **Compound 29** :

R.M.N.^{1}H δ (ppm) : 1.75 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 5.7 (s, 2H) ; 7.45 (d, 2H) ; 7.8 (d, 1H) ; 8 (d, 2H) ; 8.3 (s, 1H) ; 8.4 (d, 1H)

Solvent : $CDCl_3$

- **Compound 30** :

R.M.N.^{1}H δ (ppm) : 1.75 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 3.9 (s, 3H) ; 4 (s, 3H) ; 5.7 (s, 2H) ; 7.1 (d, 1H) ; 7.8 (d, 1H) ; 8.2 (d, 1 H) ; 8.35 (s, 1H) ; 8.45 (s, 1H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

- **Compound 31** :

R.M.N.^{1}H δ (ppm) : 2.0 – 2.1 (m, 4H) ; 3.35 – 3.45 (m, 4H) ; 5.45 (s, 2H) ; 7.2 - 7.3 (dd, 1H) ; 7.75 (d, 1H) ; 8.05 (d, 1H) ; 8.25 (d, 1H) ; 8.35 (s, 1 H) ; 8.55 (d, 1H) ; 8.9 (s, 1H)

Solvent : $CDCl_3$

- **Compound 32** :

R.M.N.^{1}H δ (ppm) : 1.7 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 5.45 (s, 2H) ; 7.25 (d, 2H) ; 7.75 (d, 2H) ; 7.9 (d, 1H) ; 8.25 (d, 1H) ; 8.45 (s, 1H)

Solvent : $CDCl_3$

- **Compound 33** :

R.M.N.^{1}H δ (ppm) : 1.7 – 2.0 (m, 8H) ; 3.3 – 3.45 (m, 4H) ; 5.4 (s, 2H) ; 6.9 – 7.0 (m, 2H) ; 7.65 - 7.75 (m, 2H) ; 7.9 (d, 1H) ; 8.3 (d, 1H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

- **Compound 34** :

R.M.N.^{1}H δ (ppm) : 1.8 – 2 (m, 8H) ; 3.35 – 3.5 (m, 4H) ; 5.5 (s, 2H) ; 7.6 (dd, 2H) ; 7.8 (dd,2H) ; 7.9 (m, 1H) ; 8.3 (dd, 1H) ; 8.5 (d, 1H)

Solvent : $CHCl_3$

- **Compound 35** :

R.M.N.^{1}H δ (ppm) : 1.7 – 2 (m, 8H) ; 3.3 – 3.45 (m, 4H) ; 3.8 (s, 3H) ; 3.85 (s, 3H) ; 5.4 (s, 2H) ; 6.8 (d, 1H) ; 7.25 – 7.35 (m, 2H) ; 7.8 (d, 1H) ; 8.3 (d, 1H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

- **Compound 36** :

R.M.N.^{1}H δ (ppm) : 1.8 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 5.45 (s, 2H) ; 7.25 (m, 1H) ; 7.9 (d, 1H) ; 8.1 (d, 1H) ; 8.35 (d, 1H) ; 8.5 (m, 2H) ; 8.95 (s, 1H)

Solvent : $CDCl_3$

- **Compound 37** :

R.M.N.^{1}H δ (ppm) : 1.7 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 5.05 (d, 2H) ; 6.45 (dt, 1H) ; 6.9 (d, 1H) ; 7.15 – 7.3 (m, 3H) ; 7.35 (d, 2H) ; 7.9 (d, 1H) ; 8.3 (d, 1H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

- **Compound 38** :

R.M.N.^{1}H δ (ppm) : 1.7 – 2 (m, 8H) ; 3.3 – 3.5 (m, 4H) ; 5.05 (d, 2H) ; 6.35 – 6.45 (m, 1H) ; 6.75 – 6.85 (d, 1H) ; 7.2 – 7.35 (m, 4H) ; 7.85 (m, 1H) ; 8.3 (m, 1H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

- **Compound 39** :

R.M.N.^{1}H δ (ppm) : 1.7 – 1.95 (m, 8H) ; 3.3 – 3.45 (m, 4H) ; 3.75 (s, 3H) ; 5.05 (m, 2H) ; 6.25 – 6.35 (m, 1H) ; 6.8 (m, 3H) ; 7.3 (m, 2H) ; 7.85 (m, 1H) ; 8.3 (m, 1H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

- **Compound 40** :

R.M.N.^{1}H δ (ppm) : 1.7 – 2 (m, 8H) ; 3.3 – 3.5 (m, 4H) ; 5.05 (d, 2H) ; 6.45 – 6.55 (m, 1H) ; 6.85 (d, 1H) ; 7.2 (m, 1H) ; 7.65 (m, 1H) ; 7.9 (m, 1H) ; 8.35 (d, 1H) ; 8.45 (m, 1H) ; 8.5 (d, 1H) ; 8.6 (d, 1H)

Solvent : $CDCl_3$

- **Compound 41** :

R.M.N.^{1}H δ (ppm) : 1.7 – 2 (m, 8H) ; 3.3 – 3.5 (m, 4H) ; 5.05 (d, 2H) ; 6.55 – 6.7 (m, 1H) ; 6.8 (d, 1H) ; 7.2 (d, 2H) ; 7.9 (m, 1H) ; 8.3 (d, 1H) ; 8.5 (m, 3H)

Solvent : $CDCl_3$

- **Compound 42** :

R.M.N.^{1}H δ (ppm) : 2 - 2.1 (m, 4H) ; 2.3 (s, 3H) ; 3.3 – 3.45 (m, 4H) ; 5.4 (s, 2H) ; 7.1 (d, 2H) ; 7.6 (d, 2H) ; 7.8 (d, 1H) ; 8.1 (d, 1H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

- **Compound 43** :

R.M.N.^{1}H δ (ppm) : 1.9 – 2.05 (m, 4H) ; 3.25 – 3.4 (m, 4H) ; 5.35 (s, 2H) ; 7.2 (d, 2H) ; 7.6 (d, 2H) ; 7.8 (d, 1H) ; 8.1 (d, 1H) ; 8.4 (s, 1H)

Solvent : $CDCl_3$

- **Compound 44** :

R.M.N.^{1}H δ (ppm) : 2.0 – 2.1 (m, 4H) ; 3.35 – 3.45 (m, 4H) ; 5.4 (s, 2H) ; 6.9 – 7.0 (m, 2H) ; 7.6 – 7.7 (m, 2H) ; 7.85 (d, 1H) ; 8.1 (d, 1H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

- **Compound 45** :

R.M.N.^{1}H δ (ppm) : 2 – 2.15 (m, 4H) ; 3.35 – 3.5 (m, 4H) ; 5.45 (s, 2H) ; 7.45 (t, 1H) ; 7.55 (d, 1H) ; 7.85 – 8.0 (m, 3H) ; 8.2 (d, 1H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

- **Compound 46** :

R.M.N.^{1}H δ (ppm) : 1.95 – 2.1 (m, 4H) ; 3.35 – 3.5 (m, 4H) ; 5.45 (s, 2H) ; 7.6 (d, 2H) ; 7.8 (d, 2H) ; 7.9 (d, 1H) ; 8.15 (d, 1H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

- **Compound 47** :

R.M.N.^{1}H δ (ppm) : 2 – 2.1 (m, 4H) ; 3.35 – 3.45 (m, 4H) ; 3.9 (s, 3H) ; 5.5 (s, 2H) ; 7.7 (d, 2H) ; 7.9 (d, 1H) ; 8.0 (d, 2H) ; 8.15 (d, 1H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

- **Compound 48** :

R.M.N.^{1}H δ (ppm) : 2 – 2.15 (m, 4H) ; 3.3 – 3.45 (m, 4H) ; 5.5 (s, 2H) ; 7.75 - 7.9 (m, 3H) ; 8.1 – 8.2 (m, 3H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

- **Compound 49** :

R.M.N.^{1}H δ (ppm) : 2 – 2.15 (m, 4H) ; 3.35 – 3.5 (m, 4H) ; 3.75 (s, 3H) ; 5.4 (s, 2H) ; 6.8 (d, 2H) ; 7.65 (d, 2H) ; 7.8 (d, 1H) ; 8.15 (d, 1H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

- **Compound 50** :

R.M.N.^{1}H δ (ppm) : 2 – 2.15 (m, 4H) ; 2.25 (s, 3H) ; 3.35 – 3.45 (m, 4H) ; 5.45 (s, 2H) ; 7.0 (d, 2H) ; 7.75 (d, 2H) ; 7.85 (d, 1H) ; 8.15 (d, 1H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

- **Compound 51** :

R.M.N.^{1}H δ (ppm) : 1.9 – 2.1 (m, 4H) ; 3.2 – 3.45 (m, 4H) ; 5.2 (s, 2H) ; 6.7 (d, 2H) ; 7.35 (d, 2H) ; 8 (d, 1H) ; 8.2 (d, 1H) ; 8.3 (s, 1H) ; 9.25 (s, 1H)

Solvent : $CDCl_3$

- **Compound 52** :

R.M.N.^{1}H δ (ppm) : 2.0 – 2.1 (m, 4H) ; 3.35 – 3.45 (m, 4H) ; 3.85 (s, 3H) ; 3.9 (s, 3H) ; 5.4 (s, 2H) ; 6.8 (d, 1H) ; 7.2 – 7.35 (m, 2H) ; 7.8 (d, 1H) ; 8.15 (d, 1H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

- **Compound 53** :

R.M.N.^{1}H δ (ppm) : 2.0 – 2.1 (m, 4H) ; 3.3 – 3.4 (m, 4H) ; 5.35 (s, 2H) ; 5.9 (s, 2H) ; 6.7 (d, 1H) ; 7.15 – 7.3 (m, 2H) ; 7.85 (d, 1H) ; 8.1 (d, 1H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

Compound 54 :

R.M.N.^{1}H δ (ppm) : 2 – 2.1 (m, 4H) ; 3.35 – 3.4 (m, 4H) ; 3.75 (s, 6H) ; 5.4 (s, 2H) ; 6.35 (s, 1H) ; 6.8 (s, 2H) ; 7.85 (d, 1H) ; 8.2 (d, 1H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

- **Compound 55** :

R.M.N.^{1}H δ (ppm) : 2 – 2.1 (m, 4H) ; 3.35 – 3.45 (m, 4H) ; 3.8 (s, 3H) ; 3.85 (s, 6H) ; 5.4 (s, 2H) ; 7 (s, 2H) ; 7.85 (d, 1H) ; 8.2 (d, 1H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

- **Compound 56** :

R.M.N.^{1}H δ (ppm) : 1.95 - 2.1 (m, 4H) ; 3.25 – 3.45 (m, 4H) ; 3.55 (s, 2H) ; 5.4 (s, 2H) ; 7.25 (d, 2H) ; 7.35 (d, 2H) ; 8.15 (d, 1H) ; 8.2 (d, 1H) ; 8.35 (s, 1H) ; 12.2 – 12.5 (m, 1H)

Solvent : $CDCl_3$

- **Compound 57** :

R.M.N.^{1}H δ (ppm) : 2.1 (m, 4H) ; 3.4 (m, 4H) ; 5.05 (d, 2H) ; 6.4 (dt, 1H) ; 6.9 (d, 1H) ; 7.15 – 7.3 (m, 3H) ; 7.35 (d, 2H) ; 7.9 (d, 1H) ; 8.15 (d, 1H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

- **Compound 58** :

R.M.N.^{1}H δ (ppm) : 2.0 – 2.15 (m, 4H) ; 3.35 – 3.5 (m, 4H) ; 5.2 (d, 2H) ; 5.7 – 5.8 (m, 1H) ; 6.7 (d, 1H) ; 7.2 – 7.45 (m, 5H) ; 7.9 (d, 1H) ; 8.2 (d, 1H) ; 8.6 (s, 1H)

Solvent : $CDCl_3$

- **Compound 59** :

R.M.N.^{1}H δ (ppm) : 2.05 (m, 4H) ; 3.4 (m, 4H) ; 5 (d, 2H) ; 6.4 (m, 1H) ; 6.85 (d, 1H) ; 7.15 – 7.3 (m, 4H) ; 7.85 (m, 1H) ; 8.15 (d, 1H) ; 8.45 (s, 1H)

Solvent : $CDCl_3$

- **Compound 60** :

R.M.N.^{1}H δ (ppm) : 1.95 – 2.10 (m, 4H) ; 3.4 (m, 4H) ; 3.75 (s, 3H) ; 4.95 (m, 2H) ; 6.25 – 6.35 (m, 1H) ; 6.75 – 6.9 (m, 3H) ; 7.2 – 7.3 (m, 2H) ; 7.85 (m, 1H) ; 8.15 (m, 1H) ; 8.45 (m, 1H)

Solvent : $CDCl_3$

- **Compound 61** :

R.M.N.^{1}H δ (ppm) : 1.95 – 2.15 (m, 4H) ; 3.3 – 3.5 (m, 4H) ; 5.05 (m, 2H) ; 6.45 – 6.55 (m, 1H) ; 6.75 – 6.9 (d, 1H) ; 7.2 (m, 1H) ; 7.6 – 7.7 (m, 1H) ; 7.85 – 7.95 (m, 1H) ; 8.15 (m, 1H) ; 8.4 (m, 1H) ; 8.5 (m, 1H) ; 8.6 (m, 1H)

Solvent : $CDCl_3$

- **Compound 62** :

R.M.N.^{1}H δ (ppm) : 1.9 – 2.05 (m, 4H) ; 3.3 – 3.45 (m, 4H) ; 5.05 (d, 2H) ; 6.55 – 6.7 (m, 1H) ; 6.8 (d, 1H) ; 7.25 (m, 2H) ; 7.9 (m, 1H) ; 8.2 (m, 1H) ; 8.45 - 8.55 (m, 3H)

Solvent : $CDCl_3$

- **Compound 63** :

R.M.N.^{1}H δ (ppm) : 1.8 – 1.9 (m, 2H) ; 3.25 (m, 2H) ; 5.1 (s, 2H) ; 6.9 (s, 1H) ; 7.4 (s, 1H) ; 8 (d, 1H) ; 8.1 (d, 1H) ; 8.2 (s, 1H) ; 11. 8 (m, 1H)

Solvent : DMSO

- **Compound 64** :

R.M.N.^{1}H δ (ppm) : 2.05 – 2.15 (m, 4H) ; 2.4 (s, 3H) ; 2.6 (s, 3H) ; 3.4 (m, 4H) ; 5.2 (s, 2H) ; 7.9 (d, 1H) ; 8.2 (d, 1H) ; 8.4 (s, 1H)

Solvent : $CDCl_3$

- **Compound 65** :

R.M.N.^{1}H δ (ppm) : 1.25 – 1.75 (m, 8H) ; 1.9 – 2.05 (m, 4H) ; 2.5 – 2.7 (m, 1H) ; 3.3 – 3.4 (m, 4H) ; 4.2 (d, 2H) ; 7.8 (d, 1H) ; 8.1 (d, 1H) ; 8.45 (s, 1H)

Solvent : $CDCl_3$

- **Compound 66** :

R.M.N.^{1}H δ (ppm) : 1 (t, 3H) ; 1.4 – 1.55 (m, 2H) ; 1.8 – 1.9 (m, 2H) ; 2.0 – 2.1 (m, 4H) ; 3.4 – 3.5 (m, 4H) ; 4.3 (t, 2H) ; 7.9 (d, 1H) ; 8.2 (d, 1H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

- **Compound 67** :

R.M.N.^{1}H δ (ppm) : 2 – 2.15 (m, 4H) ; 3.35 – 3.5 (m, 4H) ; 5.0 (q, 2H) ; 7.9 (d, 1H) ; 8.2 (d, 1H) ; 8.55 (s, 1H)

Solvent : $CDCl_3$

- **Compound 68** :

R.M.N.^{1}H δ (ppm) : 2 (m, 4H) ; 3.15 (m, 1H) ; 3.3 (m, 4H) ; 4.05 (m, 2H) ; 4.5 (m, 2H) ; 7.08 (m, 1H) ; 8.15 (m, 1H) ; 8.4 (s, 1H)

Solvent : $CDCl_3$

- **Compound 69** :

R.M.N.^{1}H δ (ppm) : 1.1 (t, 6H) ; 2.0 – 2.1 (m, 4H) ; 2.65 (q, 4H) ; 2.9 (t, 2H) ; 3.35 – 3.45 (m, 4H) ; 4.4 (t, 2H) ; 7.9 (d, 1H) ; 8.2 (d, 1H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

- **Compound 70** :

R.M.N.^{1}H δ (ppm) : 2 – 2.15 (m, 4H) ; 2.3 (s, 1H) ; 3.35 – 3.5 (m, 4H) ; 5.1 (s, 2H) ; 7.9 (d, 1H) ; 8.2 (d, 1H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

- **Compound 71** :

R.M.N.^{1}H δ (ppm) : 2.1 (m, 4H) ; 3.4 (m, 4H) ; 4.45 (m, 2H) ; 4.75 (m, 2H) ; 6.9 (m, 3H) ; 7.2 – 7,3 (m, 2H) ; 7.9 (m, 1H) ; 8. 2 (m, 1H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

- **Compound 72 :**

R.M.N.^{1}H δ (ppm) : 2.1 (m, 4H) ; 3.45 (m, 6H) ; 4.6 (m, 2H) ; 7.1 (m, 1H) ; 7.2 (m, 2H) ; 7.4 (m, 2H) ; 7.85 (m, 1H) ; 8.1 (m, 1H) ; 8.45 (s, 1H)

Solvent : $CDCl_3$

- **Compound 73 :**

R.M.N.^{1}H δ (ppm) : 1.9 - 2.05 (m, 4H) ; 3.3 - 3.4 (m, 4H) ; 3.08 (s, 3H) ; 6.7 (s, 1H) ; 7.2 – 7.35 (m, 3H) ; 7.7 – 7.85 (m, 3H) ; 8.1 (d, 1H) ; 8.4 (s, 1H)

Solvent : $CDCl_3$

- **Compound 74 :**

R.M.N.^{1}H δ (ppm) : 1.4 – 1.6 (m, 1H) ; 1.7 - 2 (m, 5H) ; 3 – 3.1 (m, 2H) ; 3.3 – 3.4 (m, 2H) ; 5.5 (s, 2H) ; 7.6 (d, 2H) ; 7.8 (d, 2H) ; 7.9 (d, 1H) ; 8.3 (d, 1H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

- **Compound 75 :**

R.M.N.^{1}H δ (ppm) : 1.4 (m, 1H) ; 1.7 – 1.95 (m, 5H) ; 3 – 3.1 (m, 2H) ; 3.3 – 3.4 (m, 2H) ; 3.8 (s, 3H) ; 3.9 (s, 3H) ; 5.4 (s, 2H) ; 6.8 (d, 1H) ; 7.25 – 7.35 (m, 2H) ; 7.9 (d, 1H) ; 8.3 (d, 1H) ; 8.40 (s, 1H)

Solvent : $CDCl_3$

- **Compound 76 :**

R.M.N.^{1}H δ (ppm) : 1.35 – 2.1 (m, 6H) ; 3.05 (t, 2H) ; 3.35 (m, 2H) ; 5.1 (d, 2H) ; 6.5 (dt, 1H) ; 6.9 (d, 1H) ; 7.1 – 7.5 (m, 5H) ; 7.9 (d, 1H) ; 8.3 (d, 1H) ; 8.55 (s, 1H)

Solvent : $CDCl_3$

- **Compound 77 :**

R.M.N.^{1}H δ (ppm) : 2.9 (m, 4H) ; 3.45 (m, 2H) ; 3.6 (m, 2H) ; 5.1 (m, 2H) ; 6.5 (m, 1H) ; 6.85 (d, 1H) ; 7.2 (m, 1H) ; 7.65 (m, 1H) ; 7.9 (m, 1H) ; 8.25 (m, 1H) ; 8.45 (m, 1H) ; 8.5 (m, 1H) ; 8.55 (s, 1H)

Solvent : $CDCl_3$

- **Compound 78 :**

R.M.N.^{1}H δ (ppm) : 2.3 (s, 3H) ; 2.9 (s, 6H) ; 5.4 (s, 2H) ; 7.1 (d, 2H) ; 7.6 (d, 2H) ; 7.85 (d, 1H) ; 8.2 (d, 1H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

- **Compound 79 :**

R.M.N.^{1}H δ (ppm) : 2.95 (s, 6H) ; 5.45 (s, 2H) ; 7.55 (d, 2H) ; 7.75 (d, 2H) ; 7.9 (d, 1H) ; 8.2 (d, 1H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

- **Compound 80 :**

R.M.N.^{1}H δ (ppm) : 2.85 (s, 6H) ; 5.2 (s, 2H) ; 6.7 (d, 2H) ; 7.3 (d, 2H) ; 8 (d, 1H) ; 8.2 – 8.3 (m, 2H) ; 9.3 (s, 1H)

Solvent : $CDCl_3$

- **Compound 81 :**

R.M.N.^{1}H δ (ppm) : 2.9 (s, 6H) ; 3.9 (s, 3H) ; 5.45 (s, 2H) ; 7.7 (m, 2H) ; 7.85 (m, 1H) ; 7.9 (m, 2H) ; 8.2 (d, 1H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

- **Compound 82 :**

R.M.N.^{1}H δ (ppm) : 2.85 (s, 6H) ; 3.6 (s, 2H) ; 5.35 (s, 2H) ; 7.25 (d, 2H) ; 7.5 (d, 2H) ; 8.15 (d, 1H) ; 8.3 (d, 1H) ; 8.35 (s, 1H) ; 12.2 – 12.45 (m, 1H)

Solvent : DMSO

- **Compound 83 :**

R.M.N.^{1}H δ (ppm) : 2.9 (s, 6H) ; 3.7 (s, 2H) ; 5.45 (s, 2H) ; 7.25 (m, 2H) ; 7.7 (m, 2H) ; 7.85 (m, 1H) ; 8.2 (d, 1H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

- **Compound 84 :**

R.M.N.^{1}H δ (ppm) : 2.9 (s, 6H) ; 5.5 (s, 2H) ; 7.25 (m, 1H) ; 7.85 (m, 1H) ; 8.05 (m, 1H) ; 8.25 (d, 1H) ; 8.5 (m, 2H) ; 8.9 (s, 1H)

Solvent : $CDCl_3$

- **Compound 85 :**

R.M.N.^{1}H δ (ppm) : 2.9 (s, 6H) ; 5.05 (d, 2H) ; 6.4 – 6.55 (dt, 1H) ; 6.9 (d, 1H) ; 7.2 – 7.4 (m, 5H) ; 7.9 (d, 1H) ; 8.25 (d, 1H) ; 8.55 (s, 1H)

Solvent : $CDCl_3$

- **Compound 86 :**

R.M.N.^{1}H δ (ppm) : 2.95 (s, 6H) ; 5.29 (d, 2H) ; 5.7 – 5.8 (m, 1H) ; 6.7 (d, 1H) ; 7.2 – 7.45 (m, 5H) ; 7.9 (d, 1H) ; 8.25 (d, 1H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

- **Compound 87 :**

R.M.N.^{1}H δ (ppm) : 2.9 (s, 6H) ; 5.05 (d, 2H) ; 6.55 – 6.7 (m, 1H) ; 6.85 (d, 1H) ; 7.2 (m, 2H) ; 7.85 (m, 1H) ; 8.25 (d, 1H) ; 8.5 (m, 3H)

Solvent : $CDCl_3$

- **Compound 88 :**

R.M.N.^{1}H δ (ppm) : 2.8 (s, 6H) ; 3.2 (s, 1H) ; 4.9 (s, 2H) ; 8.1 (m, 1H) ; 8.2 (d, 1H) ; 8.3 (s, 1H)

Solvent : DMSO

- **Compound 89 :**

R.M.N.^{1}H δ (ppm) : 2.9 (s, 6H) ; 5.2 (s, 2H) ; 7.2 (m, 3H) ; 7.4 (m, 2H) ; 7.85 (m, 1H) ; 8.2 (d, 1H) ; 8.55 (s, 1H)

Solvent : $CDCl_3$

- **Compound 90 :**

R.M.N.^{1}H δ (ppm) : 2.95 (s, 6H) ; 3.85 (s, 3H) ; 6.8 (s, 1H) ; 7.3 – 7.4 (m, 3H) ; 7.75 – 7.9 (m, 3H) ; 8.2 (d, 1H) ; 8.5 (s, 1H)

Solvent : $CDCl_3$

- **Compound 91 :**

R.M.N.^{1}H δ (ppm) : 1.75 – 1.9 (m, 8H) ; 2.5 (s, 3H) ; 3.4 – 3.5 (m, 4H) ; 5.5 (s, 2H) ; 7.2 – 7.3 (dd, 1H) ; 7.6 – 7.65 (d, 1H) ; 8.05 – 8.01 (d, 1H) ; 8.2 (s, 1H) ; 8.3 – 8.35 (d, 1H) ; 8.55 (d, 1H) ; 8.95 (s, 1H)

Solvent : $CDCl_3$

- **Compound 92:**

R.M.N.^{1}H δ (ppm) : 1.75 – 2 (m, 8H) ; 2.5 (s, 3H) ; 3.4 – 3.5 (m, 4H) ; 5.1 (d, 1H) ; 5.4 – 5.55 (dt, 1H) ; 6.9 – 7 (d, 1H) ; 7.2 – 7.3 (m, 4H) ; 7.4 (d, 2H) ; 7.6 (d, 1H) ; 8.2 (s, 1H) ; 8.3 (d, 1H)

Solvent : $CDCl_3$

- **Compound 93 :**

R.M.N.^{1}H δ (ppm) : 2 – 2.1 (m, 4H) ; 2.5 (s, 3H) ; 3.3 – 3.4 (m, 4H) ; 5.5 (s, 2H) ; 7.6 (m, 3H) ; 7.8 (d, 2H) ; 8.1 – 8.2 (m, 2H)

Solvent : $CDCl_3$

- **Compound 94 :**

R.M.N.^{1}H δ (ppm) : 2 – 2.1 (m, 4H) ; 2.5 (s, 3H) ; 3.4 – 3.5 (m, 4H) ; 3.8 (s, 3H) ; 3.9 (s, 3H) ; 5.4 (s, 2H) ; 6.8 (d, 1H) ; 7.3 - 7.4 (m, 2H) ; 7.5 (d, 1H) ; 8.1 – 8.2 (m, 2H)

Solvent : $CDCl_3$

- **Compound 95 :**

R.M.N.^{1}H δ (ppm) : 2.1 – 2.2 (m, 4H) ; 2.5 (s, 3H) ; 3.4 – 3.5 (m, 4H) ; 3.9 (s, 3H) ; 5.5 (s, 2H) ; 7.6 (m, 1H) ; 7.7 (m, 2H) ; 7.95 - 8 (m, 2H) ; 8.1 – 8.2 (m, 2H)

Solvent : $CDCl_3$

- **Compound 96 :**

R.M.N.^{1}H δ (ppm) : 2 (m, 4H) ; 2.5 (s, 3H) ; 3.3 – 3.4 (m, 4H) ; 3.6 (s, 2H) ; 5.3 (s, 2H) ; 7.3 (m, 2H) ; 7.45 (m, 2H) ; 7.8 (m, 2H) ; 8.1 (s, 1H) ; 8.2 (d, 2H) ; 12.4 (m, 1H)

Solvent : DMSO

- **Compound 97 :**

R.M.N.^{1}H δ (ppm) : 1.95 (m, 4H) ; 2.5 (s, 3H) ; 3.35 (m, 4H) ; 5.4 (s, 2H) ; 7.35 (dd, 1H) ; 7.55 (d, 1H) ; 8.05 (s, 1H) ; 8.15 (d, 1H) ; 8.5 (d, 1H) ; 8.7 (s, 1H)

Solvent : DMSO

- **Compound 98 :**

R.M.N.^{1}H δ (ppm) : 2 – 2.1 (m, 4H) ; 2.45 (s, 3H) ; 3.3 – 3.45 (m, 4H) ; 5.05 (d, 2H) ; 6.4 – 6.5 (dt, 1H) ; 6.85 – 6.95 (d, 1H) ; 7.1 – 7.45 (m, 5H) ; 7.6 (d, 1H) ; 8.1 – 8.2 (m, 2H)

Solvent : $CDCl_3$

- **Compound 99 :**

R.M.N.^{1}H δ (ppm) : 2.4 – 3.75 (m, 13H) ; 5.35 (s, 2H) ; 7.1 – 7.5 (m, 4H) ; 7.8 (d, 1H) ; 8.1 (s, 1H) ; 8.25 (d, 1H)

Solvent : DMSO

- **Compound 100 :**

R.M.N.^{1}H δ (ppm) : 2.5 (s, 3H) ; 2.9 (m, 4H) ; 3.45 (m, 2H) ; 3.65 (m, 2H) ; 5.1 (m, 2H) ; 6.5 (m, 1H) ; 6.85 (d, 1H) ; 7.2 (m, 1H) ; 7.6 (m, 1H) ; 7.7 (m, 1H) ; 8.2 (m, 2H) ; 8.45 (d, 1H) ; 8.6 (1s, 1H)

Solvent : $CDCl_3$

- **Compound 101 :**

R.M.N.^{1}H δ (ppm) : 2.5 (s, 3H) ; 2.95 (s, 6H) ; 5.5 (s, 2H) ; 7.6 (m, 3H) ; 7.8 (m, 2H) ; 8.15 – 8.25 (m, 2H)

Solvent : $CDCl_3$

- **Compound 102 :**

R.M.N.^{1}H δ (ppm) : 2.2 (s, 3H) ; 2.6 (s, 6H) ; 3.25 (s, 2H) ; 5.1 (s, 2H) ; 7 (m, 2H) ; 7.15 (m, 2H) ; 7.5 (m, 1H) ; 7.8 (s, 1H) ; 8 (d, 1H) ; 12 (m, 1H)

Solvent : DMSO

- **Compound 103** :

R.M.N.^{1}H δ (ppm) : 2.5 (s, 3H) ; 3 (s, 6H) ; 5.1 (d, 2H) ; 6.4 – 6.5 (dt, 1H) ; 6.9 (d, 1H) ; 7.15 – 7.4 (m, 6H) ; 7.6 (d, 1H) ; 8.2 (m, 1H)

Solvent : $CDCl_3$

- **Compound 104** :

R.M.N.^{1}H δ (ppm) : 2.5 (s, 3H) ; 2.95 (s, 6H) ; 5.1 (d, 2H) ; 6.45 – 6.55 (dt, 1H) ; 6.8 – 6.85 (d, 1H) ; 7.2 (m, 1H) ; 7.6 (dd, 1H) ; 7.7 (dd, 1H) ; 8.2 – 8.25 (m, 2H) ; 8.4 (d, 1H) ; 8.6 (s, 1H)

Solvent : $CDCl_3$

- **Compound 105** :

R.M.N.^{1}H δ (ppm) : 2.5 (s, 3H) ; 2.95 (s, 6H) ; 5.1 (d, 2H) ; 6.6 – 6.7 (dt, 1H) ; 6.8 (d, 1H) ; 7.2 (d, 2H) ; 7.6 (d, 1H) ; 8.2 – 8.25 (dd, 2H) ; 8.5 (d, 2H)

Solvent : $CDCl_3$

- **Compound 106** :

R.M.N.^{1}H δ (ppm) : 1.7 - 2 (m, 8H) ; 2.55 (m, 3H) ; 3.35 – 3.6 (m, 4H) ; 5.1 (d, 2H) ; 6.45 (dt, 1H) ; 6.85 (d, 1H) ; 7.1 – 7.45 (m, 6H) ; 8.25 (m, 2H)

Solvent : $CDCl_3$

- **Compound 107** : R.M.N.^{1}H δ (ppm) : 2.9 (d, 6H) ; 5.5 (s, 2H) ; 7.6 (m, 2H) ; 7.7 (m, 2H) ; 8.0 (m, 1H) ; 8.4 (m, 1H) ; 8.7 (s, 1H)

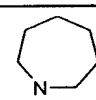
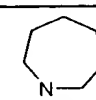
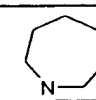
Solvent : $CDCl_3$

- **Compound 108** :

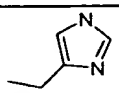
R.M.N.^{1}H δ (ppm) : 1.9 (m, 4H) ; 3.25 (m, 4H) ; 6.85 (d, 2H) ; 6.3 – 6.4 (dt, 1H) ; 6.6 – 6.7 (d, 1H) ; 7.15 – 7.3 (m, 4H) ; 7.35 – 7.4 (d, 2H) ; 7.5 (s, 1H) ; 8.05 (d, 1H) ; 10.1 (m, 1H),

Solvent : DMSO

TABLE 2

N° Compound	X1	R	NR4R5	Yield (%)	MP (°C)	Method
109	H	(E) C6H5CH=CHCH2		28	176	A
110	7-Cl	CH2=CHCH2		24	173	A
111	7-Cl	C6H5CH2		58	148	A
112	7-Cl	4-CH3C6H4CH2		50	182	A
113	7-Cl	2-ClC6H4CH2		77	228	A
114	7-Cl	3-ClC6H4CH2		31	166	A
115	7-Cl	4-ClC6H4CH2		60	245	A
116	7-Cl	4-BrC6H4CH2		38	244	A
117	7-Cl	4-FC6H4CH2		42,5	224	A
118	7-Cl	4-CF3C6H4CH2		39	232	A
119	7-Cl	4-CNC6H4CH2		46	> 260	A
120	7-Cl	2-(OCH3)C6H4CH2		57	184	A
121	7-Cl	3-(OCH3)C6H4CH2		46	163	A
122	7-Cl	4-(OCH3)C6H4CH2		32,5	164-165	A
123	7-Cl	3,4-Cl2C6H3CH2		60	212	A

N° Compound	X1	R	NR4R5	Yield (%)	MP (°C)	Method
124	7-Cl	3,4-(OCH3)2C6H3CH2		39	153	A
125	7-Cl	(2-pyridyl)CH2		9	153	A
126	7-Cl	(3-pyridyl)CH2		8	184	C
127	7-Cl	C6H5CH2CH2		7	196	A
128	7-Cl	4(CH3O)C6H4(CH2)2		61	196	A
129	7-Cl	C6H5(CH2)3		36	130	A
130	7-Cl	C6H5C(=O)CH2		38,5	230-232	A
131	7-Cl	4(CH3O)C6H4C(=O)CH2		42	238	A
132	7-Cl	4-ClC6H4C(=O)CH2		59	238	A
133	7-Cl	4(CH3O)-3-(COOCH3)-C6H3C(=O)CH2		30	136	A
134	7-Br	4-ClC6H4CH2		57	247	A
135	7-Br	4-FC6H4CH2		54	216	A
136	7-Br	4-CNC6H4CH2		53	293	A
137	7-Br	3,4-(CH3O)2C6H3CH2		61	174	A
138	7-Br	4-(CH2COOH)C6H4CH2		1	269	B
139	7-Br	(3-pyridyl)CH2		4	192	C
140	7-Br	(E) C6H5CH=CHCH2		70	198	A
141	7-Br	(Z) C6H5CH=CHCH2		57	187	A
142	7-Br	4-ClC6H4CH2		18	185	A

N° Compound	X1	R	NR4R5	Yield (%)	MP (°C)	Method
143	7-Br	4-FC6H4CH2		16	233	A
144	7-Br	4-CNC6H4CH2		52	222	A
145	7-Br	4-(COOCH3)C6H4CH2		31	193	A
146	7-Br	4-(CH3O)C6H4CH2		14	164	B
147	7-Br	4-(OCOCH3)C6H4CH2		24	199	B
148	7-Br	4-OHC6H4CH2		15	283	B
149	7-Br	3,4-(OCH2O)C6H4CH2		57	234	A
150	7-Br	3,5-(CH3O)2C6H4CH2		21	168	A
151	7-Br	3,4,5-(CH3O)3C6H2CH2		21	199-201	A
152	7-Br			4	-	B
153	7-Br	n-butyl		13	130	B
154	7-Br	CH(C6H5)COOCH3		55	187	A
155	7-Br	(E) C6H5CH=CHCH2		10	206	B
156	7-Br	CH(C6H5)COOCH3		32	83	B
157	7-CH3	(E) C6H5CH=CHCH2		43	193	A
158	7-CH3	(E) C6H5CH=CHCH2		35	225	A
159	8-CH3	CH3		70	-	A

N° Compound	X1	R	NR4R5	Yield (%)	MP (°C)	Method
160	8-CH3	(E) C6H5CH=CHCH2		18	-	A
161	7-OH	(E) C6H5CH=CHCH2		10	255	A
162	7- 	(E) C6H5CH=CHCH2		28	-	A

Compound 109 :

N.M.R.^{1}H δ (ppm) : 1.7 – 1.85 (m. 8H) ; 3.3 – 3.45 (m. 4H) ; 5.85 (d. 2H) ; 6.35 – 6.45 (dt. 1H) ; 6.65 – 6.75 (d. 1H) ; 7.25 (t. 1H) ; 7.35 (t. 1H) ; 7.45 (d. 1H) ; 7.6 (t. 1H) ; 7.85 (t. 1H) ; 8.2 (d. 1H) ; 8.3 (d. 1H)

Solvent : $CDCl_3$

- **Compound 110 :**

N.M.R.^{1}H δ (ppm) : 1.65 – 1.95 (m. 8H) ; 3.35 (m. 4H) ; 4.8 (d. 2H) ; 5.25 – 5.4 (m. 2H) ; 5.9 – 6.1 (m. 1H) ; 7.55 – 8.4 (m. 3H)

Solvent : $CDCl_3$

- **Compound 111 :**

N.M.R.^{1}H δ (ppm): 1.7 – 1.9 (m. 8H) ; 3.35 (m. 4H) ; 5.25 (s. 2H) ; 7.2 – 7.4 (m. 3H) ; 7.45 (d. 2H) ; 7.6 (d. 1H) ; 8.15 (d. 1H) ; 8.4 (s. 1H)

Solvent : $CDCl_3$

- **Compound 112 :**

N.M.R.^{1}H δ (ppm) : 1.7 – 1.9 (m. 8H) ; 2.3 (s. 3H) ; 3.35 (m. 4H) ; 5.25 (s. 2H) ; 7.1 – 8.45 (m. 7H)

Solvent : $CDCl_3$

- **Compound 113 :**

N.M.R.^{1}H δ (ppm) : 1.7 – 1.95 (m. 8H) ; 3.4 (m. 4H) ; 5.45 (s. 2H) ; 7.15 – 7.3 (m. 3H) ; 7.4 (d. 1H) ; 7.65 (d. 1H) ; 8.2 (d. 1H) ; 8.45 (s. 1H)

Solvent : $CDCl_3$

- **Compound 114** :

N.M.R.^{1}H δ (ppm) : 1.7 – 1.9 (m. 8H) ; 3.4 (m. 4H) ; 5.25 (s. 2H) ; 7.2 – 7.4 (m. 3H) ; 7.45 (s. 1H) ; 7.6 (d. 1H) ; 8.15 (d. 1H) ; 8.45 (s. 1H)

Solvent : $CDCl_3$

- **Compound 115** :

N.M.R.^{1}H δ (ppm) : 1.65 – 1.85 (m. 8H) ; 3.3 (m. 4H) ; 5.15 (s. 2H) ; 7.25 (d. 2H) ; 7.35 (d. 2H) ; 7.55 (d. 1H) ; 8.05 (d. 1H) ; 8.3 (s. 1H)

Solvent : $CDCl_3$

- **Compound 116** :

N.M.R.^{1}H δ (ppm) : 1.7 – 1.95 (m. 8H) ; 3.35 (m. 4H) ; 5.25 (d. 2H) ; 7.35 (d. 2H) ; 7.45 (d. 2H) ; 7.6 (d. 1H) ; 8.1 (d. 1H) ; 8.4 (s. 1H)

Solvent : $CDCl_3$

- **Compound 117** :

N.M.R.^{1}H δ (ppm) : 1.7 – 1.9 (m. 8H) ; 3.35 (m. 4H) ; 5.35 (s. 2H) ; 7.5 – 7.7 (m. 5H) ; 8.15 (d. 1H) ; 8.4 (s. 1H)

Solvent : $CDCl_3$

- **Compound 118** :

N.M.R.^{1}H δ (ppm) : 1.7 – 1.9 (m. 8H) ; 3.4 (m. 4H) ; 5.35 (s. 2H) ; 7.5 – 7.7 (m. 5H) ; 8.1 (d. 1H) ; 8.4 (s. 1H)

Solvent : $CDCl_3$

- **Compound 119** :

N.M.R.^{1}H δ (ppm) : 1.7 – 1.9 (m. 8H) ; 3.4 (m. 4H) ; 3.9 (s. 3H) ; 5.35 (s. 2H) ; 6.9 (m. 2H) ; 7.2 (d. 1H) ; 7.3 (t. 1H) ; 7.6 (d. 1H) ; 8.2 (d. 1H) ; 8.4 (s. 1H)

Solvent : $CDCl_3$

- **Compound 120** :

N.M.R.^{1}H δ (ppm) : 1.7 – 2.0 (m. 8H) ; 3.35 (m. 4H) ; 3.75 (s. 3H) ; 5.4 (s. 2H) ; 6.8 (m. 1H) ; 7.15 – 7.3 (m. 3H) ; 7.7 (d. 1H) ; 8.35 (m. 2H)
Solvent : $CDCl_3$

- **Compound 121** :
N.M.R.^{1}H δ (ppm) : 1.7 – 1.9 (m. 8H) ; 3.35 (m. 4H) ; 3.8 (s. 3H) ; 5.2 (s. 2H) ; 6.85 (d. 2H) ; 7.45 (d. 2H) ; 7.65 (d. 1H) ; 8.15 (d. 1H) ; 8.45 (s. 1H)
Solvent : $CDCl_3$

- **Compound 122** :
N.M.R.^{1}H δ (ppm) : 1.7 – 1.9 (m. 8H) ; 3.4 (m. 4H) ; 5.2 (s. 2H) ; 7.3 (d. 1H) ; 7.4 (d. 1H) ; 7.5 (s. 1H) ; 7.6 (d. 1H) ; 8.15 (d. 1H) ; 8.4 (s. 1H)
Solvent : $CDCl_3$

- **Compound 123** :
N.M.R.^{1}H δ (ppm) : 1.7 – 1.9 (m. 8H) ; 3.4 (m. 4H) ; 3.85 (s. 3H) ; 3.90 (s. 3H) ; 5.2 (s. 2H) ; 6.85 (d. 1H) ; 7.1 (m. 2H) ; 7.65 (d. 1H) 8.2 (d. 1H) ; 8.45 (s. 1H)
Solvent : $CDCl_3$

- **Compound 124** :
N.M.R.^{1}H δ (ppm) : 1.65 – 195 (m. 8H) ; 3.4 (m. 4H) ; 5.45 (s. 2H) ; 7.2 (m. 1H) ; 7.3 (d. 1H) ; 7.65 (m. 2H) ; 8.2 (d. 1H) ; 8.4 (s. 1H) ; 8.55 (d. 1H)
Solvent : $CDCl_3$

- **Compound 125** :
N.M.R.^{1}H δ (ppm) : 1.7 – 1.95 (m. 8H) ; 3.4 (m. 4H) ; 5.3 (s. 2H) ; 7.25 (m. 1H) ; 7.6 (d. 1H) ; 7.85 (d. 1H) ; 8.15 (d. 1H) ; 8.45 (s. 1H) ; 8.6 (d. 1H) ; 8.75 (s. 1H)
Solvent : $CDCl_3$

- **Compound 126** :
N.M.R.^{1}H δ (ppm) : 1.55 – 1.9 (m. 8H) ; 3.1 (t. 2H) ; 3.25 (m. 4H) ; 4.25 (t. 2H) ; 7.05 – 7.25 (m.5H) ; 7.55 (d. 1H) ; 8.1 (d. 1H) ; 8.35 (s. 1H)
Solvent : $CDCl_3$

- **Compound 127** :

N.M.R.^{1}H δ (ppm) : 1.75 – 1.9 (m. 8H) ; 3.15 (t. 2H) ; 3.35 (m. 4H) ; 3.75 (s. 3H) ; 4.35 (t. 2H) ; 6.8 (d. 2H) ; 7.15 (d. 2H) ; 7.6 (d. 1H) ; 8.15 (d. 1H) ; 8.4 (s. 1H)

Solvent : $CDCl_3$

- **Compound 128** :

N.M.R.^{1}H δ (ppm) : 1.7 – 1.95 (m. 8H) ; 2.2 (m. 2H) ; 2.7 (t. 2H) ; 3.35 (m. 4H) ; 4.2 (t. 2H) ; 7 – 7.3 (m. 5H) ; 7.65 (d. 1H) ; 8.1 (d. 1H) ; 8.45 (s. 1H)

Solvent : $CDCl_3$

- **Compound 129** :

N.M.R.^{1}H δ (ppm) : 1.7 – 1.9 (m. 8H) ; 3.4 (m. 4H) ; 3.9 (s. 3H) ; 5.6 (s. 2H) ; 7.0 (d. 2H) ; 7.7 (d. 1H) ; 8 (d. 2H) ; 8.25 (d. 1H) ; 8.45 (s. 1H)

Solvent : $CDCl_3$

- **Compound 130** :

N.M.R.1H δ (ppm) : 1.6-1.9(m.8H) ; 3.4(m.4H) ; 5.8(s.2H) ; 7.6(t.2H) ; 7.75(t.1H) ; 7.95(d.1H) ; 8.1(m.3H) ; 8.3(d.1H)

Solvent : DMSO

- **Compound 131** :

N.M.R.^{1}H δ (ppm) : 1.7 – 1.95 (m. 8H) ; 3.4 (m. 4H) ; 5.55 (s. 2H) ; 7.45 (d. 2H) ; 7.65 (d. 1H) ; 7.9 (d. 2H) ; 8.2 (d. 1H) ; 8.4 (s. 1 H)

Solvent : $CDCl_3$

- **Compound 132** :

N.M.R.^{1}H δ (ppm) : 1.7 – 1.9 (m. 8H) ; 3.4 (m. 4H) ; 3.9 (s. 3H) ; 4.0 (s. 3H) ; 5.6 (s. 2H) ; 7.1 (d. 1H) ; 7.7 (d. 1H) ; 8.1 (d. 1H) ; 8.2 (d. 1 H) ; 8.4 (m. 2H)

Solvent : $CDCl_3$

- **Compound 133** :

N.M.R.^{1}H δ (ppm) : 1.75 – 1.9 (m. 8H) ; 3.4 (m. 4H) ; 3.9 (s. 3H) ; 4.0 (s. 3H) ; 5.6 (s. 2H) ; 7.1 (m. 1H) ; 7.7 (m. 1H) ; 8.15 –8.45 (m. 4H)

Solvent : $CDCl_3$

- **Compound 134:**

N.M.R.^{1}H δ (ppm) : 1.75 – 1.9 (m. 8H) ; 3.35 (m. 4H) ; 5.25 (s. 2H) ; 7.25 - 8.6 (m. 7 H)

Solvent : $CDCl_3$

- **Compound 135 :**

N.M.R.^{1}H δ (ppm) : 1.65 – 1.95 (m. 8H) ; 3.3 – 3.45 (m. 4H) ; 5.25 (s. 2H) ; 6.95 – 7.1 (m. 2H) ; 7.4 – 7.55 (m. 2H) ; 7.8 (d. 1H) ; 8.1 (d. 1H) ; 8.6 (s. 1H)

Solvent : $CDCl_3$

- **Compound 136 :**

N.M.R.^{1}H δ (ppm) : 1.75 – 1.95 (m. 8H) ; 3.3 – 3.45 (m. 4H) ; 5.3 (s. 2H) ; 7.5 – 7.7 (m. 4H) ; 7.8 (m. 1H) ; 8.1 (dd. 1H) ; 8.6 (s. 1H)

Solvent : $CDCl_3$

- **Compound 137 :**

N.M.R.^{1}H δ (ppm) : 1.7 – 1.9 (m. 8H) ; 3.25 – 3.4 (m. 4H) ; 3.8 (s. 3H) ; 3.82 (s. 3H) ; 5.2 (s. 2H) ; 6.8 (d. 1H) ; 7.05 – 7.1 (m. 2H) ; 7.75 (d. 1H) ; 8.05 (d. 1H) ; 8.6 (s. 1H)

Solvent : $CDCl_3$

- **Compound 138 :**

N.M.R.^{1}H δ (ppm) : 1.6 – 1.85 (m. 8H) ; 3.2 - 3.4 (bs. 4H) ; 3.55 (s. 2H) ; 5.2 (s. 2H) ; 7.2 (m. 2H) ; 7.3 (m. 2H) ; 8 (m. 1H) ; 8.2 (m. 1H) ; 8.25 (s. 1H) ; 12.3 (bs. 1H)

Solvent : DMSO

- **Compound 139 :**

N.M.R.^{1}H δ (ppm) : 1.75 – 1.9 (m. 8H) ; 3.4 (m. 4H) ; 5.35 (s. 2H) ; 7.3 (m. 1H) ; 7.8 (d. 1H) ; 7.9 (d. 1H) ; 8.1 (d. 1H) ; 8.65 (m. 2H) ; 8.8 (s. 1H)

Solvent : $CDCl_3$

- **Compound 140 :**

N.M.R.^{1}H δ (ppm) : 1.8 – 1.95 (m. 8H) ; 3.4 (m. 4H) ; 4.9 (d. 2H) ; 6.35 (m. 1H) ; 6.75 (d. 1H) ; 7.25 – 7.45 (m. 5H) ; 7.8 – 8.65 (m. 3H)

Solvent : $CDCl_3$

- **Compound 141** :

N.M.R.^{1}H δ (ppm) : 1.35 – 2.05 (m. 6H) ; 2.95 (t. 2H) ; 3.4 (d. 2H) ; 4.9 (d. 2H) ; 6.35 (dt. 1H) ; 6.75 (d. 1H) ; 7.25 – 7.45 (m. 5H) ; 7.85 (d. 1H) ; 8.15 (d. 1H) ; 8.65 (s. 1H)

Solvent : $CDCl_3$

- **Compound 142** :

N.M.R.^{1}H δ (ppm) : 2 – 2.1 (m. 4H) ; 3.3 - 3.4 (m. 4H) ; 5.25 (s. 2H) ; 7.25 (d. 2H) ; 7.4 (d. 2H) ; 7.75 (d. 1H) ; 7.95 (d. 1H) ; 8.55 (s. 1H)

Solvent : $CDCl_3$

- **Compound 143** :

N.M.R.^{1}H δ (ppm) : 1.95 – 2.1 (m. 4H) ; 3.3 - 3.45 (m. 4H) ; 5.2 (s. 2H) ; 6.95 – 7.1 (m. 2H) ; 7.35 – 7.5 (m. 2H) ; 7.75 (d. 1H) ; 7.95 (d. 1H) ; 8.6 (s. 1H)

Solvent : $CDCl_3$

- **Compound 144** :

N.M.R.^{1}H δ (ppm) : 2 – 2.15 (m. 4H) ; 3.3 - 3.45 (m. 4H) ; 5.3 (s. 2H) ; 7.55 – 7.7 (m. 4H) ; 7.8 – 7.9 (d. 1H) ; 8.0 (d. 1H) ; 8.6 (s. 1H)

Solvent : $CDCl_3$

- **Compound 145** :

N.M.R.^{1}H δ (ppm) : 2 – 2.1 (m. 4H) ; 3.3 - 3.4 (m. 4H) ; 3.9 (s. 3H) ; 5.3 (s. 2H) ; 7.5 (d. 2H) ; 7.8 (d. 1H) ; 7.9 – 8.05 (m. 3H) ; 8.6 (s. 1H)

Solvent : $CDCl_3$

- **Compound 146** :

N.M.R.^{1}H δ (ppm) : 2 – 2.1 (m. 4H) ; 3.3 - 3.4 (m. 4H) ; 3.8 (s. 3H) ; 5.2 (s. 2H) ; 6.9 (d. 2 H) ; 7.45 (d. 2H) ; 7.8 (d. 1H) ; 7.95 (d. 1H) ; 8.6 (s. 1H)

Solvent : $CDCl_3$

- **Compound 147** :

N.M.R.^{1}H δ (ppm) : 2 – 2.1 (m. 4H) ; 2.3 (s. 3H) ; 3.3 – 3.4 (m. 4H) ; 5.25 (s. 2H) ; 7.05 (d. 2H) ; 7.5 (d. 2H) ; 7.8 (d. 1H) ; 8.0 (d. 1H) ; 8.6 (s. 1H)

Solvent : $CDCl_3$

- **Compound 148** :

N.M.R.^{1}H δ (ppm) : 2.7 (s. 6H) ; 5 (s. 2H) ; 6.6 (d. 2H) ; 7.1 (d. 2H) ; 7.9 (d. 1H) ; 8.0 (d. 1H) ; 8.1 (s. 1H) ; 9.35 (s. 1H)

Solvent : $CDCl_3$

- **Compound 149** :

N.M.R.^{1}H δ (ppm) : 2 – 2.15 (m. 4H) ; 3.3 - 3.45 (m. 4H) ; 5.15 (s. 2H) ; 5.9 (s. 2H) ; 6.75 (d. 1H) ; 6.9 – 7.0 (m. 2H) ; 7.8 (d. 1H) ; 7.9 (d. 1H) ; 8.6 (s. 1H)

Solvent : $CDCl_3$

- **Compound 150** :

N.M.R.^{1}H δ (ppm) : 2.0 – 2.1 (m. 4H) ; 3.3 - 3.4 (m. 4H) ; 3.75 (s. 6H) ; 5.2 (s. 2H) ; 6.4 (s. 1H) ; 6.65 (s. 2H) ; 7.8 (d. 1H) ; 7.95 (d. 1H) ; 8.65 (s. 1H)

Solvent : $CDCl_3$

- **Compound 151** :

N.M.R.^{1}H δ (ppm) : 2.0 – 2.1 (m. 4H) ; 3.3 - 3.4 (m. 4H) ; 3.85 (s. 3H) ; 3.9 (s. 6H) ; 5.2 (s. 2H) ; 6.8 (s. 2H) ; 7.8 (d. 1H) ; 7.95 (d. 1H) ; 8.65 (s. 1H)

Solvent : $CDCl_3$

- **Compound 152** :

N.M.R.^{1}H δ (ppm) : 2 (m. 4H) ; 3.35 (m. 4H) ; 5.2 (s. 2H) ; 7.15 (s. 1H) ; 7.6 (s. 1H) ; 8 – 8.15 (m. 2H) ; 8.3 (s. 1H) ; 12 (m. 1H)

Solvent : DMSO

- **Compound 153** :

N.M.R.^{1}H δ (ppm) : 0.95 (t. 3H) ; 1.35 – 1.5 (m. 2H) ; 1.8 – 1.9 (m. 2H) ; 2.0 – 2.1 (m. 4H) ; 3.4 - 3.5 (m. 4H) ; 4.1 (t. 2H) ; 7.8 (d. 1H) ; 8.0 (d. 1H) ; 8.6 (s. 1H)

Solvent : $CDCl_3$

- **Compound 154** :

N.M.R.^{1}H δ (ppm) : 2.45 – 2.55 (m. 4H) ; 3.25 - 3.4 (m. 4H) ; 3.7 (s. 3H) ; 6.6 (s. 1H) ; 7.35 – 7.50 (m. 3H) ; 7.55 (d. 2H) ; 8 – 8.1 (m. 2H) ; 8.3 (s. 1H)

Solvent : DMSO

- **Compound 155** :

N.M.R.^{1}H δ (ppm) : 2.9 (s. 6H) ; 4.8 (d. 2H) ; 6.2 – 6.3 (dt. 1H) ; 6.7 (d. 1H) ; 7.1 – 7.35 (m. 5H) ; 7.75 (d. 1H) ; 8.0 (d. 1H) ; 8.6 (s. 1H)

Solvent : $CDCl_3$

- **Compound 156** :

N.M.R.^{1}H δ (ppm) : 2.9 (s. 6H) ; 3.8 (s. 3H) ; 6.6 (s. 1H) ; 7.35 – 7.45 (m. 3H) ; 7.55 (d. 2H) ; 7.8 (d. 1H) ; 8 (d. 1H) : 8.6 (s. 1H)

Solvent : $CDCl_3$

- **Compound 157** :

N.M.R.^{1}H δ (ppm) : 1.8 – 1.95 (m. 8H) ; 2.5 (s. 3H) ; 3.4 – 3.5 (m. 4H) ; 4.9 (d. 2H) ; 6.3 – 6.45 (dt. 1H) ; 6.7 – 6.8 (d. 1H) ; 7.2 – 7.3 (m. 3H) ; 7.35 (d. 2H) ; 7.55 (d. 2H) ; 8.1 (d. 1H) ; 8.3 (s. 1H)

Solvent : $CDCl_3$

- **Compound 158** :

N.M.R.^{1}H δ (ppm) : 2.1 (m. 4H) ; 2.5 (s. 3H) ; 3.4 (m. 4H) ; 4.9 (d. 2H) ; 6.3 – 6.45 (dt. 1H) ; 6.7 – 6.8 (d. 1H) ; 7.2 – 7.4 (m. 5H) ; 7.5 (m. 1H) ; 8 (d. 1H) ; 8.3 (d. 1H)

Solvent : $CDCl_3$

- **Compound 159** :

N.M.R.^{1}H δ (ppm) : 1.7 – 1.9 (m. 8H) ; 2.45 (s. 3H) ; 3.25 – 3.35 (m. 4H) ; 3.65 (s. 3H) ; 7.2 – 7.3 (m. 2H) ; 8 (m. 1H) ; 8.2 - 8.3 (m. 1H)

Solvent : $CDCl_3$

- **Compound 160** :

N.M.R.^{1}H δ (ppm) : 1.8 – 2 (m. 8H) ; 2.55 (s. 3H) ; 3.3 - 3.5 (m. 4H) ; 4.9 (m. 2H) ; 6.3 – 6.4 (m. 1H) ; 6.7 – 6.8 (d. 1H) ; 7.2 – 7.4 (m. 6H) ; 8.1 (s. 1H) ; 8.35 (m. 1H)

Solvent : $CDCl_3$

- **Compound 161** :

N.M.R.^{1}H δ (ppm) : 2 (m. 4H) ; 3.4 (m. 4H) ; 4.8 (d. 2H) ; 6.35 – 6.4 (dt. 1H) ; 6.7 (d. 1H) ; 7.2 – 7.4 (m. 4H) ; 7.45 (d. 2H) ; 7.55 (s. 1H) ; 8 (d. 1H) ; 10 (m. 1H)

Solvent : $CDCl_3$

- **Compound 162** :

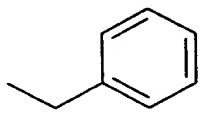
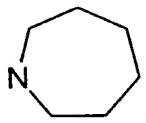
N.M.R.^{1}H δ (ppm) : 1.5 – 2.1 (m. 16H) ; 3.3 - 3.7 (m. 8H) ; 4.9 (d. 2H) ; 6.3 – 6.4 (dt. 1H) ; 6.7 – 6.8 (d. 1H) ; 6.8– 6.9 (d. 1H) ; 7.2 – 7.5 (m. 6H) ; 8.25 (d. 1H)

Solvent : $CDCl_3$

Example 163

METHOD A : 1-Azepanyl-4-benzyl-7-bromo-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

(I) : X1 = 7-Br ; X2 = H ;

R =  ; NR4R5 = 

In a 50 ml balloon flask protected from humidity, we resuspend 4.0 g (10,7 mmol) of 4-benzyl-1,7-dibromo-4H-[1,2,4] triazolo [4,3-a]quinazolin-5-one (prepared by method of example 256) 25 ml of hexamethylene imine.

The mixture is then heated by reflux, under shaking, for 16 hours.

After cooling down, the obtained solution is concentrated under vacuum to give 4.8 g of residue which is purified by flash chromatography on silica column, by elution with the mixture CH_2Cl_2 99.6 / CH_3OH 0.4.

The fractions pure in CCM are joined, evaporated until dry and the obtained product (4.0 g) is recrystallized in ethanol.

We obtain 3.2 g of compound from example 163 as crystals.

Yield = 66 %.

F (Tottoli) = 175° C

CCM (CH_2Cl_2 99 / CH_3OH 1) : Rf = 0.40

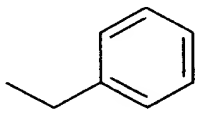
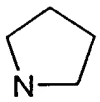
NMR ^1H δ (ppm) CDCl3 :

1.7 – 1.85 (m. 8H) ; 3.3 (m. 4H) ; 5.3 (s. 2H) ; 7.2 – 7.35 (m. 3H) ; 7.45 –d. 2H) ; 8.0 (d. 1H) ; 8.15 (s. 1H) ; 8.4 (d. 1H)

Example 164

METHOD B : 1-(Pyrrolidin-1-yl)-4-benzyl-7-bromo-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

(I) : X1 = 7-Br ; X2 = H ;

R =  ; NR4R5 = 

In a reactor protected from humidity, we resuspend 37.0 g (85 mmol) of 4-benzyl-1,7-dibromo-4H-[1,2,4] triazolo [4,3-a]quinazolin-5-one in 750 ml of dimethylformamide (DMF) and add 14.3 g (340 mmol) of sodium bicarbonate then 12.1 g (340 mmol) of pyrrolidine.

The mixture is then heated by reflux, under shaking, for 6 hours.

After cooling down, the solvent is evaporated under vacuum, the obtained residue is resuspended in a mixture water / ethyl acetate and the insoluble fraction is triturated then filtered and dried : we obtain then from a first round 18.3g of compound from example 164, this compound being pure by CCM.

The aqueous and organic phases are separated, the ethyl acetate phase is washed in water and dried on Na_2SO_4. After solvent concentration under vacuum, we obtain from a second round 14.2g of compound from example 164, also pure by CCM.

Yield (as crude product) = 90% ; the product will be used like this in the next step.

A 0.35g sample is recrystallized in methanol to give 0.32g of pure compound as crystal.

F (Tottoli) = 173°C

CCM (CH2Cl2 99 / CH3OH 1) = 0.35

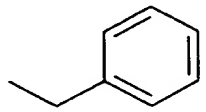
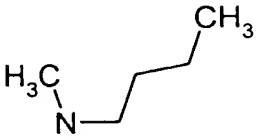
N.M.R.^1H δ (ppm) : 2.1 (m. 4H) ; 3.4 (m. 4H) ; 5.45 (s. 2H) ; 7.3 (m. 3H) ; 7.65 (d. 2H) ; 7.85 (d. 1H) ; 8.15 (d. 1H) ; 8.45 (s. 1H)

Solvent : $CDCl_3$

Example 165

METHOD C : 1-[N-(n-butyl), N-methylamino]-4-benzyl-7-bromo-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

(I) : X1 = 7-Br ; X2 = H

R =  ; NR4R5 = 

In a pressure reactor, we resuspend 2.5 g (5,75 mmol) of 4-benzyl-1,7-dibromo-4H-[1,2,4] triazolo [4,3-a]quinazolin-5-one in 30 ml of ethanol. We add 5.0g of n-butyl-methylamine (57.5 mmol), we hermetically seal the reactor then we heat in an oil bath at 160°C for 8 hours. After cooling down and leaving aside for 2 days, the residual oil (2.8g) is chromatographied on silica column by elution with the mixture CH_2Cl_2 99.5 – CH_3OH 0.5. We obtain 1.8 g of compound from example 165.

Yield = 70 %.

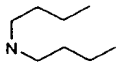
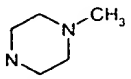
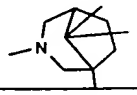
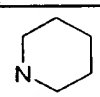
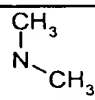
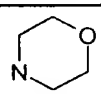
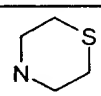
CCM (CH_2 Cl_2 98.5 / CH_3 OH 1.5) : Rf = 0.45

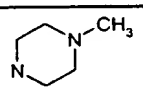
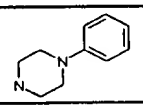
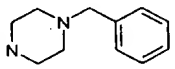
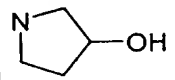
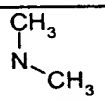
N.M.R.^{1}H δ (ppm) : 0.9 (t. 3H) ; 1.25 – 1.4 (m. 2H) ; 1.55 – 1.7 (m. 2H) ; 2.85 (s. 3H) ; 2.9 – 3.5 (m. 2H) ; 5.5 (s. 2H) ; 7.2 – 7.35 (m. 3H) ; 7.7 (d. 2H) ; 7.9 (d. 1H) ; 8.25 (d. 1H) ; 8.5 (s. 1H)

Solvent : $CDCl_3$

The compounds (I) from examples 166 to 198 (table 3) are prepared according to one of the methods A, B or C described in examples 163 to 165.

TABLE3

N° Compound	X1	R	NR4R5	Yld (%)	MP (°C)	Method
166	H	C6H5CH2		70	167	B
167	7-Cl	CH3		17	112	A
168	7-Cl	CH3		35	192	A
169	7-Cl	CH3		50	180-182	A
170	7-Cl	CH3		60	185	A
171	7-Cl	C6H5		5	179	A
172	7-Cl	C6H5CH2		88	162	A
173	7-Cl	C6H5CH2		78	163	B
174	7-Cl	C6H5CH2		68	178	B
175	8-Cl	CH3		11	179	A
176	8-Cl	C6H5CH2		1	-	B
177	7-Br	CH3		72	174	A
178	7-Br	C6H5CH2		67	183-185	A
179	7-Br	C6H5CH2		53	171	B
180	7-Br	C6H5CH2		50	189	B
181	7-Br	C6H5CH2		49	235	B

N° Compound	X1	R	NR4R5	Yld (%)	MP (°C)	Method
182	7-Br	C6H5CH2		60	230	B
183	7-Br	C6H5CH2		51	238	B
184	7-Br	C6H5CH2		50	226	B
185	7-Br	C6H5CH2		82	172	B
186	7-Br	C6H5CH2		85	210	B
187	7-Br	C6H5CH2		79	176	B
188	7-Br	C6H5CH2	NHCH3	52	238	C
189	7-I	C6H5CH2		100	184	B
190	7-CH3	C6H5CH2		90	183	B
191	7-CH3	C6H5CH2		60	189	B
192	7-CH3	C6H5CH2		75	186	B
193	7-CH3	C6H5CH2		78	265	B
194	8-CH3	C6H5CH2		50	202	A
195	7-OCH3	C6H5CH2		42	153	B
196	7-OCH3	C6H5CH2		65	154	B
197	7-CN	C6H5CH2		77	219	B
198	7-NO2	C6H5CH2		32	206	A

- **Compound 166** :

N.M.R.^{1}H δ (ppm) : 2 (m. 4H) ; 3.3 (m. 4H) ; 5.35 (s. 2H) ; 7.2 – 7.3 (m. 3H) ; 7.4 (d. 2H) ; 7.6 (t. 1H) ; 7.9 (t. 1H) ; 8.2 (m. 2H)

Solvent : DMSO

- **Compound 167** :

N.M.R.^{1}H δ (ppm) : 0.8 (m. 6H) ; 1.15 – 1.25 (m. 4H) ; 1.35 – 1.55 (m. 4H) ; 3 (m. 2H) ; 3.2 (m. 2H) ; 3.7 (s. 3H) ; 7.65 (m. 1H) ; 8.3 (m. 1H) ; 8.45 (m. 1H)

Solvent : $CDCl_3$

- **Compound 168 :**

N.M.R.1H δ (ppm) : 1.3-1.9 (m. 6H) ; 2.9 (t. 2H) ; 3.3 (m. 2H) ; 3.5 (s. 3H) ; 8.0 (d. 1H) ; 8.1 (d. 1H) ; 8.3 (d. 1H)

Solvent : CDCl3

- **Compound 170 :**

N.M.R.1H δ (ppm) : 0.7 (s. 3H) ; 0.8 (s. 3H) ; 1.0 (s. 3H) ; 1.5-1.9 (m. 5H) ; 2.55 (d. 1H) ; 2.85 (d. 1H) ; 3.15 (m. 4H) ; 3.4 (m. 4H) ; 7.9 (d. 1 H) ; 8.0 (s. 1H) ; 8.4 (m. 1H)

Solvent : DMSO

- **Compound 171** :

N.M.R.^{1}H δ (ppm) : 1.7 – 1.8 (m. 8H) ; 3.3 (m. 4H(+H_2O) ; 7.45 – 7.6 (m. 5H) ; 8.05 (m. 1H) ; 8.15 (s. 1H) ; 8.45 (d. 1H)

Solvent : DMSO

- **Compound 172** :

N.M.R.^{1}H δ (ppm) : 1.7 – 1.85 (m. 8H) ; 3.3 (s. 4H) ; 5.3 (s. 2H) ; 7.25 – 7.5 (m. 5H) ; 8.0 (m. 1H) ; 8.15 (d. 1H) ; 8.4 (d. 1H)

Solvent : DMSO

- **Compound 173** :

N.M.R.^{1}H δ (ppm) : 2.05 (m. 4H) ; 3.4 (m. 4H) ; 5.45 (s. 2H) ; 7.2 – 7.35 (m. 3H) ; 7.65 – 7.75 (m. 3H) ; 8.2 (dd. 1H) ; 8.35 (s. 1H)

Solvent : $CDCl_3$

- **Compound 174** :

N.M.R.^{1}H δ (ppm) : 1.4 – 1.6 (m. 1H) ; 1.7 - 2 (m. 4H) ; 3 - 3.15 (m. 2H) ; 3.3 – 3.45 (m. 2H) ; 5.45 (s. 2H) ; 7.25 – 7.35 (m. 3H) ; 7.7 – 7.8 (m. 3H) ; 8.3 – 8.4 (m. 2H)

Solvent : $CDCl_3$

- **Compound 175** :

N.M.R.^{1}H δ (ppm) : 1.85 – 1.95 (m. 4H) ; 3.4 (m. 4H + H_2O) ; 3.65 (s. 3H) ; 7.7 (d. 1H) ; 8.3 (d. 1H) ; 8 .55 (s. 1H)

Solvent : DMSO

- **Compound 176** :

N.M.R.^{1}H δ (ppm) : 1.8 – 2 (m. 8H) ; 3.3 – 3.5 (m. 4H) ; 5.4 (s. 2H) ; 7.2 – 7.35 (m. 3H) ; 7.4 – 7.45 (m. 2H) ; 7.65 – 7.7 (m. 2H) ; 8.25 –8.3 (m. 2H) ; 8.6 (s. 1H)

Solvent : $CDCl_3$

- **Compound 177** :

N.M.R.^{1}H δ (ppm) : 1.7 – 1.85 (m. 8H) ; 3.4 (m. 4H) ; 3.7 (s. 3H) ; 7.75 (m. 1H) ; 8.25 (m. 1H) ; 8.4 (m. 1H)

Solvent : $CDCl_3$

- **Compound 178** :

N.M.R.^{1}H δ (ppm) : 1.35 – 1.95 (m. 6H) ; 3.05 (t. 2H) ; 3.35 (d. 2H) ; 5.45 (s. 2H) ; 7.3 (m. 3H) ; 7.75 (d. 2H) ; 7.95 (d. 1H) ; 8.3 (d. 1H) ; 8.5 (s. 1H)

Solvent : $CDCl_3$

- **Compound 179** :

N.M.R.^{1}H δ (ppm) : 2.9 (s. 6H) ; 5.5 (s. 2H) ; 7.25 – 7.35 (m. 3H) ; 7.7 (d. 2H) ; 7.85 (d. 1H) ; 8.2 (d. 1H) ; 8.5 (s. 1H)

Solvent : $CDCl_3$

- **Compound 180** :

N.M.R.^{1}H δ (ppm) : 3.2 – 3.4 (m. 4H) ; 3.75 – 3.9 (m. 2H) ; 3.9 – 4.1 (m. 2H) ; 5.5 (s. 2H) ; 7.2 – 7.35 (m. 3H) ; 7.7 (d. 2H) ; 7.9 (d. 1H) ; 8.25 (d. 1H) ; 8.5 (s. 1H)

Solvent : $CDCl_3$

- **Compound 181** :

N.M.R.^{1}H δ (ppm) : 2.8 – 3.0 (m. 4H) ; 3.35 – 3.5 (m. 2H) ; 3.5 – 3.7 (m. 2H) ; 5.45 (s. 2H) ; 7.2 – 7.35 (m. 3H) ; 7.7 (d. 2H) ; 7.9 (d. 1H) ; 8.2 (d. 1H) ; 8.5 (s. 1H)

Solvent : $CDCl_3$

- **Compound 182** :

N.M.R.^{1}H δ (ppm) : 2.3 – 2.45 (m. 5H) ; 2.9 – 3.0 (m. 2H) ; 3.25 – 3.35 (m. 4H) ; 5.5 (s. 2H) ; 7.2 – 7.35 (m. 3H) ; 7.7 (d. 2H) ; 7.9 (d. 1H) ; 8.25 (d. 1H) ; 8.5 (s. 1H)

Solvent : $CDCl_3$

- **Compound 183** :

N.M.R.^{1}H δ (ppm) : 3.0 – 3.2 (m. 2H) ; 3.35 – 3.5 (m. 4H) ; 3.6 – 3.75 (m. 2H) ; 5.5 (s. 2H) ; 6.9 – 7.05 (m. 3H) ; 7.2 – 7.35 (m. 5H) ; 7.7 (d. 2H) ; 7.85 (d. 1H) ; 8.3 (d. 1H) ; 8.55 (s. 1H)

Solvent : $CDCl_3$

- **Compound 184** :

N.M.R.^{1}H δ (ppm) : 2.4 (m. 2H) ; 3 (m. 2H) ; 3.3 (m. 4H) ; 5.5 (s. 2H) ; 7.3 (m. 8H) ; 7.7 (m. 2H) ; 7.9 (d. 1H) ; 8.2 (d. 1H) ; 8.5 (s. 1H)

Solvent : $CDCl_3$

- **Compound 185** :

N.M.R.^{1}H δ (ppm) : 2.2 – 2.65 (m. 2H) ; 3.2 – 3.9 (m. 4H) ; 5.45 (s. 2H) ; 5.8 – 5.9 (m. 1H) ; 5.9 – 6.0 (m. 1H) ; 7.2 – 7.35 (m. 3H) ; 7.7 (d. 2H) ; 7.9 (d. 1H) ; 8.25 (d. 1H) ; 8.5 (s. 1H)

Solvent : $CDCl_3$

- **Compound 186** :

N.M.R.^{1}H δ (ppm) : 4.3 (s. 4H) ; 5.5 (s. 2H) ; 5.95 (s. 2H) ; 7.25 – 7.4 (m. 3H) ; 7.7 (d. 2H) ; 7.9 (d. 1H) ; 8.25 (d. 1H) ; 8.5 (s. 1H)

Solvent : $CDCl_3$

- **Compound 187** :

N.M.R.^{1}H δ (ppm) : 2 - 2.1 (m. 1H) ; 2.3 – 2.4 (m. 1H) ; 3.2 – 3.6 (m. 5H) ; 4.6 – 4.7 (m. 1H) ; 5.45 (s. 2H) ; 7.2 – 7.3 (m. 3H) ; 7.65 (d. 1H) ; 7.85 (d. 1H) ; 8.3 (d. 2H) ; 8.5 (s. 1H)

Solvent : $CDCl_3$

- **Compound 188** :

N.M.R.^{1}H δ (ppm) : 3.05 (s. 3H) ; 3.9 – 4.0 (m. 1H) ; 5.35 (s. 2H) ; 7.15 – 7.25 (m. 3H) ; 7.6 (d. 2H) ; 7.7 (d. 1H) ; 7.95 (d. 1H) ; 8.4 (s. 1H)

Solvent : $CDCl_3$

- **Compound 189** :

N.M.R.^{1}H δ (ppm) : 2 (m. 4H) ; 3.4 (m. 4H) ; 5.3 (s. 2H) ; 7.3 (m. 3H) ; 7.4 (m. 2H) ; 8.0 (m. 1H) ; 8.2 (m. 1H) ; 8.5 (m. 1H)

Solvent : DMSO

- **Compound 190** :

N.M.R.^{1}H δ (ppm) : 1.75 – 1.95 (m. 8H) ; 2.45 (s. 3H) ; 3.35 – 3.45 (m. 4H) ; 5.45 (s. 2H) ; 7.2 – 7.35 (m. 3H) ; 7.45 (dd. 1H) ; 7.7 (dd. 2H) ; 8.15 (s. 1H) ; 8.3 (d. 1H)

Solvent : $CDCl_3$

- **Compound 191** :

N.M.R.^{1}H δ (ppm) : 2 (m. 4H) ; 2.5 (s. 3H) ; 3.3 (m. 4H) ; 5.3 (s. 2H) ; 7.2 – 7.55 (m. 5H) ; 7.7 (d. 1H) ; 8 (s. 1H) ; 8.15 (d. 1H)

Solvent : $CDCl_3$

- **Compound 192** :

N.M.R.^{1}H δ (ppm) : 2.45 (s. 3H) ; 2.9 (s. 6H) ; 5.45 (s. 2H) ; 7.2 – 7.3 (m. 3H) ; 7.45 (d. 1H) ; 7.7 (d. 2H) ; 8.2 (d. 2H)

Solvent : $CDCl_3$

- **Compound 193** :

N.M.R.^{1}H δ (ppm) : 2.5 (s. 3H) ; 2.8 – 3.05 (m. 4H) ; 3.35 – 3.75 (m. 4H) ; 5.5 (s. 2H) ; 7.15 – 7.4 (m. 3H) ; 7.6 (d. 1H) ; 7.7 (d. 2H) ; 8.1 – 8.25 (m. 2H)

Solvent : $CDCl_3$

- **Compound 194** :

N.M.R.^{1}H δ (ppm) : 1.8 – 1.95 (m. 8H) ; 2.55 (s. 3H) ; 3.4 (m. 4H) ; 5.4 (s. 2H) ; 7.25 – 7.35 (m. 4H) ; 7.7 (m. 2H) ; 8.25 (m. 2H)

Solvent : $CDCl_3$

- **Compound 195** :

N.M.R.^{1}H δ (ppm) : 1.8 – 1.95 (m. 8H) ; 3.35 – 3.40 (m. 4H) ; 3.9 (s. 3H) ; 5.4 (s. 2H) ; 7.25 – 7.35 (m. 4H) ; 7.7 (dd. 2H) ; 7.8 (d. 1H) ; 8.35 (d. 1H)

Solvent : $CDCl_3$

- **Compound 196** :

N.M.R.^{1}H δ (ppm) : 2 (m. 4H) ; 3.35 (m. 4H) ; 3.9 (s. 3H) ; 5.35 (s. 2H) ; 7.25 – 7.35 (m. 3H) ; 7.45 (d. 2H) ; 7.55 (d. 1H) ; 7.7 (s. 1H) ; 8.2 (d. 1H)

Solvent : DMSO

- **Compound 197** :

N.M.R.^{1}H δ (ppm) : 2.4 (m. 4H) ; 3.2 (m. 4H) ; 5.2 (s. 2H) ; 7.1 – 7.25 (m. 3H) ; 7.35 (m. 2H) ; 8.25 (m. 2H) ; 8.5 (s. 1H)

Solvent : $CDCl_3$

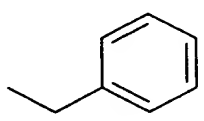
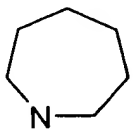
- **Compound 198** :

N.M.R.^{1}H δ (ppm) : 1.7 – 1.85 (m. 8H) ; 3.3 (s. 4H + H_2O) ; 5.35 (s. 2H) ; 7.3 (m. 3H) ; 7.5 (m. 2H) ; 8.55 (d. 1H) ; 8.75 (d. 1H) ; 8.9 (s. 1H)

Solvent : DMSO

Example 199 : 1-Azepanyl-4-benzyl-7-chloro-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

(I) ; X1 = 7-Cl ; X2 = H

R =  ; NR4R5 = 

In a 50 ml balloon flask, equipped with a shaker and refrigeration, we resuspend 0.44 g (1,27 mmol) of 4-benzyl-1,7-dichloro-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (example 254) in 2.5 ml of hexamethylene imine. Under shaking, the mixture is heated by reflux for 16 hours. The obtained brown solution is then left aside to ambient temperature until complete cooling down; then we pour in a mixture of water and methylene chloride, shake and separate the 2 phases by decantation. The organic phase is washed twice in water, dried on Na_2SO_4 then evaporated under vacuum to give 0.59 g of brown solid residue.

This is chromatographied on silica column by elution with the mixture CH_2Cl_2 99.5 / CH_3OH 0.5.

We obtain after joining and evaporation of pure by CCM fractions, 0.46 g of compound from example 199. This is recrystallized in ethanol to give 0.4 g of colorless crystal.

Yield = 77 %

F (Tottoli) = 162°C

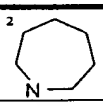
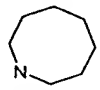
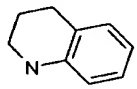
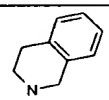
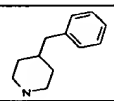
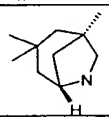
CCM (CH_2Cl_2 98.5 / CH_3OH 1.5) : Rf = 0.35

N.M.R. ^1H δ (ppm) : 1.7 – 1.85 (m. 8H) ; 3.3 (s. 4H) ; 5.3 (s. 2H) ; 7.25 – 7.5 (m. 5H) ; 8.0 (m. 1H) ; 8.15 (d. 1H) ; 8.4 (d. 1H)

Solvent : DMSO

The compounds (I) from examples 200 to 214 (table 4) are prepared according to the process from example 199.

TABLE4

N° Compound	X1	R	NR4R5	Yld (%)	MP (°C)	Method
200	H	CH3		40	199 – 203	A
201	H	C6H5CH2		66	157	A
202	6-Cl	CH3		8,5	> 275	A
203	7-Cl	CH3		77	145	A
204	7-Cl	CH3CH2		11	98-100	A
205	7-Cl	CH3		50	203-205	A
206	7-Cl	CH3		25	232	A
207	7-Cl	CH3		25	123-125	A
208	7-Cl	CH3		15	204	A
209	7-Cl	CH3		30	272	A
210	7-Cl	CH3		25	180	A
211	7-Cl	CH3		25	165	A
212	7-F	CH3		13	136	A
213	7-I	CH3		47	206	A
214	7-OCH3	CH3		34	203	A

- **Compound 200** :

N.M.R.1H δ (ppm) : 1.75-1.9 (m. 8H) ; 3.4 (m. 4H) ; 3.6 (s. 3H) ; 7.6 (t. 1H) ; 8 (t. 1H) ; 8.25 (d. 1H) ; 8.4 (d. 1H)

Solvent : DMSO

- **Compound 201** :

N.M.R.1H δ (ppm) : 1.7 - 1.85 (m. 8H) ; 3.3 (m. 4H) ; 5.3 (s. 2H) ; 7.2 - 7.35 (m. 3H) ; 7.45 (d. 2H) ; 7.6 (t. 1H) ; 7.95 (t. 1H) ; 8.2 (d. 1H) ; 8.4 (d. 1H)

Solvent : DMSO

- **Compound 202** :

N.M.R.1H δ (ppm) : 1.5 - 1.8 (m. 8H) ; 3.4 (m. 4H) ; 3.5 (s.3H) ; 7.05 (d. 1H) ; 7.5 (t. 1H) ; 8.4 (d. 1H)

Solvent : DMSO

- **Compound 203** :

N.M.R.1H δ (ppm) : 1.7 - 1.85 (m. 8H) ; 3.3 (m. 4H) ; 3.5 (s. 3H) ; 7.95 (d. 1H) ; 8.1 (s. 1H) ; 8.35 (d. 1H)

Solvent : DMSO

- **Compound 204** :

N.M.R.1H δ (ppm) : 1.3 (t. 3H) ; 1.7 - 1.9 (m. 8H) ; 3.3 (m. 4H) ; 4.15 (q. 2H) ; 7.95 (d. 1H) ; 8.1 (s. 1H) ; 8.35 (d. 1H)

Solvent : DMSO

- **Compound 205** :

N.M.R.1H δ (ppm) : 2.0 (m. 4H) ; 3.35 (m. 4H) ; 3.75 (s. 3H) ; 7.65 (d. 1H) ; 8.15 (d. 1H) ; 8.3 (s. 1H)

Solvent : CDCl3

- **Compound 206** :

N.M.R.1H δ (ppm) : 3.1 - 3.35 (m. 4H) ; 3.65 (s. 3H) ; 3.85 (m. 2H) ; 4.0 (m. 2H) ; 7.75 (d. 1H) ; 8.35 (m. 2H)

Solvent : CDCl3

- **Compound 207** :

N.M.R.1H δ (ppm) : 1.8 (m. 10H) ; 3.4 (m. 4H) ; 3.75 (s. 3H) ; 7.75 (d. 1H) ; 8.35 (s. 1H) ; 8.4 (d. 1H)

Solvent : CDCl3

- **Compound 208** :

N.M.R.1H δ (ppm) : 2.1 (m. 2H) ; 2.8 - 3.1 (m. 2H) ; 3.65 (m.1H) ; 3.75 (s.3H) ; 3.9 (m.1H) ; 6.15 (d.1H) ; 6.75 (t. 1H) ; 6.85 (t.1H) ; 7.1 (d. 1H) ; 7.5 (d. 1H) ; 7.85 (d.1H) ; 8.3 (s. 1H)

Solvent : CDCl3

- **Compound 209** :

N.M.R.1H δ (ppm) : 2.9 (m. 1H) ; 3.2 (m. 1H) ; 3.4 (m. 1H) ; 3.6 (m. 1H) ; 3.7 (s. 3H) ; 4.3 (d. 1H) ; 4.45 (d. 1H) ; 7.05 (d. 1H) ; 7.2 (m. 3H) ; 7.6 (d. 1H) ; 8.2 (d. 1H) ; 8.3 (s. 1H)

Solvent : CDCl3

- **Compound 210** :

N.M.R.1H δ (ppm) : 1.4 (m. 2H) ; 1.7 (m. 3H) ; 2.6 (d. 2H) ; 2.9 - 3.15 (m. 2H) ; 3.3-3.5 (m. 2H) ; 3.65 (s. 3H) ; 7.0-7.35 (m. 5H) ; 7.7 (d. 1H) ; 8.3 (m. 2H)

Solvent : CDCl3

- **Compound 211** :

N.M.R.1H δ (ppm) : 1 (s. 3H) ; 1.1 (s. 3H) ; 1.25-1.4 (m. 5H) ; 1.45 (d. 1H) ; 1.6 (m. 2H) ; 1.9 (d.1H) ; 2.05 (m. 1H) ; 3.35 (d.1H) ; 3.45 (d. 1H) ; 3.7 (s. 3H) ; 4 (m. 1H) ; 7.65 (d. 1H) ; 8.3 (s. 1H) ; 8.6 (d. 1H)

Solvent : CDCl3

- **Compound 212** :

N.M.R.1H δ (ppm) : 1.7 – 1.8 (m. 8H) ; 3.3 (m. 4H (+H2O)) ; 3.5 (s. 3H) ; 7.8 (m. 1H) ; 7.9 (m. 1H) ; 8.4 (m.1H)

Solvent : DMSO

- **Compound 213** :

N.M.R.1H δ (ppm) : 1.7 - 1.9 (m. 8H) ; 3.3 (m. 4H) ; 3.7 (s. 3H) ; 8.0 (d. 1H) ; 8.1 (d. 1H) ; 8.65 (s.1H)

Solvent : CDCl3

- **Compound 214** :

N.M.R.1H δ (ppm) : 1.7 - 1.85 (m. 8H) ; 3.3 (s. 4H) ; 3.5 (s. 3H) ; 3.9 (s. 3H) ; 7.5 (d. 1H) ; 7.6 (s.1H) ; 8.3 (d. 1H)

Solvent : CDCl3

Example 215 : 4-benzyl-7-bromo-1-(N-ethyl, N-methylamino)-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

0.3g (0.8 mmol) of 4-benzyl-7-bromo-1-(N-methylamino)-4H-[1,2,4] triazolo-[4,3-a]quinazolin-5-one (compound from example 188) is dissolved in 5ml of DMF. We add 0.135g (0.85 mmol) of methyl iodide and 0.13g (0.93 mmol) of potassium carbonate. The obtained mixture is shaken at ambient temperature for a night then heated at 100°C for 6 hours. After cooling down, the solvent is evaporated under vacuum, the residue is resuspended in water and ethyl acetate. The organic phase is separated by decantation, washed with a saturated solution of sodium chloride, dried on Na_2SO_4 and evaporated under vacuum. We obtain 0.3g of crude product which is purified by chromatography on silica column by elution with the mixture CH_2Cl_2 99 / CH_3OH 1. The fractions containing the desired product are joined, concentrated under vacuum then the residue is recrystallized in methanol to give 0.05g of pure compound from example 215.

Yield = 22%

F (Tottoli) = 148°C

CCM (CH_2 Cl_2 98.5 / CH_3 OH 1.5) : Rf = 0.45

N.M.R.1H δ (ppm) : 1.25 (t. 3H) ; 2.9 (s. 3H) ; 3.2 – 3.4 (m. 2H) ; 5.45 (s. 2H) ; 7.2 – 7.35 (m. 3H) ; 7.7 (d. 2H) ; 7.9 (d. 1H) ; 8.3 (d. 1H) ; 8.5 (s. 1H)

Solvent : CDCl3

Example 216 : 4-benzyl-1-(N,N-diethyl)- 7-methyl-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

2.3g (5.87 mmol) of 4-benzyl-7-methyl-1-(thiamorpholin-4-yl)-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one (compound from example 193) are resuspended in 250ml of ethanol. We add a catalytic amount of Raney 's nickel and we heat by reflux, under shaking, for 24 hours. The catalyzer is eliminated by filtration on Celite and the alcoholic solution is concentrated under vacuum : we obtain 1.6g of crude product which is purified by chromatography on

silica column by elution using CH_2Cl_2 and methanol gradient from 99.5/0.5 to give 0.9g of pure by CCM product. A sample is recrystallized in ethanol to determinate physical parameters.

Yield = 42%

F (Tottoli) = 154°C

CCM (CH_2 Cl_2 99 / CH_3 OH 1) : Rf = 0.35

N.M.R.1H δ (ppm) : 1 - 1.3 (m. 6H) ; 2.4 (s. 3H) ; 2.9 – 3.45 (m. 4H) ; 5.4 (s. 2H) ; 7.1 – 7.3 (m. 3H) ; 7.45 (d. 1H) ; 7.6 (d. 2H) ; 8.15 (s. 1H) ; 8.3 (d. 1H)

Solvent : CDCl3

Example 217 : 4-benzyl-7-bromo-1-(pyrrol-1-yl)-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

In a 25ml balloon flask, we resuspend 0.7g (1.8 mmol) of 1-amino-4-benzyl-7-bromo-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one (intermediate 10 compound of example 271) in 5ml of acetic acid. We add 0.25g (1.9 mmol) of 2.5-dimethoxytetrahydrofuran then heat the mixture by reflux for 1 hour. After cooling down and evaporation of acetic acid under vacuum, we obtain 0.8g of highly colored solid which is purified by chromatography on silica column by elution with the mixture CH_2Cl_2 / CH_3OH (99,4/0,6 then 99/1). The solid obtained from pure fractions is recrystallized in ethanol to give 0,45g of compound from example 217.

Yield = 55%

F (Tottoli) = 214°C

CCM (CH_2 Cl_2 99 / CH_3 OH 1) : Rf = 0.5

N.M.R.1H δ (ppm) : 5.55 (s. 2H) ; 5.8 (d. 1H) ; 6.5 (s. 2H) ; 6.9 (s. 2H) ; 7.25 – 7.4 (m. 3H) ; 7.7 (d. 1H) ; 7.75 (d. 2H) ; 8.55 (s. 1H)

Solvent : CDCl3

Example 218 : 4-(4-aminobenzyl)-7-bromo-1-(pyrrolidin-1-yl)-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

In a 50ml balloon flask, we resuspend 0.45g (0.96 mmol) of 7-bromo-4-(4-nitrobenzyl)-1-(pyrrol-1-yl)-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one (compound from example 48) in 10ml ethanol. We add 1.08g (24 mmol) of dehydrate stannous chloride then heat at 70°C, under shaking, for 30 minutes. After cooling down, the mixture is poured into iced water. We

extract several times by ethyl acetate with a little of $CHCl_3$, the organic phase is washed in a solution sodium chloride saturated, dried on Na_2SO_4 then concentrated under vacuum. The obtained solid residue (0.35g) is washed in methanol (50ml) to give 0.25g of pure by CCM product.

Yield = 83%

F (Tottoli) = 263°C

CCM (CH_2Cl_2 98 / CH_3OH 2) : Rf = 0.25

N.M.R.1H δ (ppm) : 1.9 - 2.05 (m. 4H) ; 3.3 – 3.4 (m. 4H) ; 5 (s. 2H) ; 5.1 (s. 2H) ; 6.5 (d. 2H) ; 7.2 (d. 2H) ; 8.1 (d. 1H) ; 8.2 (d. 1H) ; 8.3 (s. 1H)

Solvent : DMSO

Example 219 : 4-(benzyl)-7-hydroxy-1-(pyrrolidin-1-yl) -4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

Example 219-1/ 4-benzyl-7-(4-tolylsulfonyloxy-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

In a reactor equipped with a shaker and refrigeration, we resuspend 1.46g (5 mmol) of 4-benzyl-7-hydroxy-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one (intermediate obtained by method from example 255) in 15ml of dry methylene chloride. We add 0.95g (5 mmol) of tosyl chloride and then add, under shaking within 5 minutes, 1ml (7.5 mmol) of triethylamine, the reaction being slightly exothermic. After additional shaking at ambient temperature for 2 hours, the obtained organic solution is washed in water and dried on Na_2SO_4 to give, after solvent evaporation, a colored amorphous residue which is purified by chromatography on silica column by elution with ethyl acetate. We obtain 1.9g of pure product by CCM. This one will be used like this in the next step.

Yield = 85%

2/ Example 219-2/ 4-benzyl-1-bromo-7-(4-tolylsulfonyloxy-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

0.4g of this compound is obtained from 0.45g of 4-benzyl-7-(4-tolylsulfonyloxy-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one (example 219-1) by bromination method described in example 256.

Yield = 76%

3/ Example 219-3/ 4-benzyl-1-(pyrrolidin-1-yl)-7-(4-tolylsulfonyloxy)-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one and 4-benzyl-7-hydroxy-1-(pyrrolidin-1-yl)- 4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

0.83g of the brominated derived obtained in example 219-2 is treated by pyrrolidine in conditions of example 164. After treatment, we obtain 1.0g of crude mixture of 2 majoritary compounds which are separated by chromatography on silica column after elution with the mixture CH_2Cl_2 98 / CH_3OH 2. The fractions containing the first pure product are joined and concentrated to give 0.375g of 4-benzyl-1-(pyrrolidin-1-yl)-7-(4-tolylsulfonyloxy-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

Yield = 45%

The fractions containing the second pure product are joined and evaporated under vacuum to give 0.12g of 4-benzyl-7-hydroxy-1-(pyrrolidin-1-yl)-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

Yield = 15%

F (Tottoli) = 287°C

N.M.R.1H δ (ppm) : 1.95 (m. 4H) ; 3.3 (m. 4H) ; 7.3 (s. 2H) ; 7.2 – 7. 6 (m. 7H) ; 8.1 (d. 1H) ; 10.2 (s. 1H)

Solvent : DMSO

Example 220 : 4-(4-cyanobenzyl)-7-hydroxy-1-(pyrrolidin-1-yl)-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

1/ Example 220-1/ 1-(pyrrolidin-1yl)-7-(4-tolylsulfonyloxy)-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

1.3g of this compound is obtained from 2.4g of 4-benzyl-1-(pyrrolidin-1yl)-7-(4-tolylsulfonyloxy-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one (example 219-3) by debenzylation method described in example 263.

Yield = 68%

2/ Example 220-2/ 4-(4-cyanobenzyl)-1-(pyrrolidin-1-yl)-7-(4-tolylsulfonyloxy-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

0.48g of this compound is obtained from of 0.66g of 1-(pyrrolidin-1yl)-7-(4-tolylsulfonyloxy-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one (example 220-1) by N-alkylation method described in example 3.

Yield = 52%

3/ Example 220-3/ 4-(4-cyanobenzyl)-7-hydroxy-1-(pyrrolidin-1-yl)-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

0.3g (0,55 mmol) of 4-(4-cyanobenzyl)-1-(pyrrolidin-1-yl)-7-(4-tolylsulfonyloxy-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one (described in example 220-2) is dissolved in 1ml of dry DMF. We add 0.27ml of pyrrolidine (2.75 mmol) then heat at 140°C, under shaking, for 6 hours. The solvent is evaporated under vacuum and the residue is resuspended by a mixture of ethyl acetate / aqueous N hydrochloric acid solution. The insoluble residue is separated by filtration, washed in water until neutral pH and dried under vacuum ; we obtain 0.13g of crude product, which is crystallized in 5 ml of ethanol, filtered and dried to give 0.085g of pure product.

Yield = 40%

F(Tottoli) = 305°C

N.M.R.1H δ (ppm) : 2 (m. 4H) ; 3.3 (m. 4H) ; 5.35 (s. 2H) ; 7.35 (d. 1H) ; 7.6 – 7.7 (m. 3H) ; 7.8 (d. 2H) ; 8.1 (d. 1H) ; 10.2 (s. 1H)

Solvent : DMSO

Example 221 : 7-acetamido-4-benzyl-1-(pyrrolidin-1-yl) -4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

1/ Example 221-1/ 7-acetamido-4-benzyl-1-bromo -4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

0.45g of this compound is obtained from 0.5g of 7-acetamido-4-benzyl -4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one by bromination method which is described in example 256.

Yield = 72 %

2/ Example 221-2/ 7-acetamido-4-benzyl-1-(pyrrolidin-1-yl)- 4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

8.7g (21 mmol) of brominated derived which is obtained in example 221-1 are treated by 3.7 ml (42 mmol) of pyrrolidine and 3.54g (42 mmol) of sodium bicarbonate in 80 ml of DMF in conditions of example 164. After treatment, we obtain 8.0g of crude product which is purified by chromatography on silica column by elution with the mixture CH_2Cl_2 98 / CH_3OH 2. The fractions containing the pure product are joined and concentrated, then the residue is

crystallized in ethanol to give 6.6g of 7-acetamido-4-benzyl-1-(pyrrolidin-1-yl) -4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

Yield = 78 %

F(Tottoli) = 265°C

N.M.R.1H δ (ppm) : 2 – 2.1 (m. 4H) ; 2.25 (s. 3H) ; 3.4 (m. 4H) ; 5.45 (s. 2H) ; 7.2 – 7.3 (m. 3H) ; 7.6 (d. 2H) ; 8.1 (s. 1H) ; 8.2 (m. 2H) ; 8.4 (d. 1H)

Solvent : CDCl3

Example 222 : 7-acetamido-4-[(E)-3-phenylallyl]-1-(pyrrolidin-1-yl) -4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

From 1.2g (3.0 mmol) of 7-acetamido-4-benzyl-1-(pyrrolidin-1yl)-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one (described in example 221) debenzylated in 7-acetamido-1-(pyrrolidin-1yl) -4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one by Palladium/C method described in example 257, then directly treated with 0.59g of cinnamyl bromide in the presence of 0.98g cesium carbonate, in 15 ml of DMF, according to a method described in example 3. We obtain, after purification by chromatography on silica column and recrystallization in ethanol, 0.4g of pure compound from example 222.

Yield = 31 %.

F (Tottoli) = 248° C

CCM (CH_2Cl_2 95 / CH_3OH 5) : Rf = 0,30

NMR ^1H δ (ppm) CDCl3 :

2.0-2.1 (m.4H) ; 2.25 (s. 3H) ; 3.45 (m. 4H) ; 5 (d. 2H) ; 6.35-6.4(dt. 1H) ; 6.8 (d. 1H) ; 7.15-7.35 (m. 5H) ; 8.1 (s. 1H) ; 8.2-8.3 (m. 2H) ; 8.4 (m. 1H)

Example 223 : 7-amino-4-[(E)-3-phenylallyl]-1-(pyrrolidin-1-yl) -4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

In a 20 ml balloon flask, we resuspend 0.2g (0.46 mmol) of 7-acetamido-4-[(E)-3-phenylallyl]-1-(pyrrolidin-1-yl) -4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one (described in example 222) in 5 ml of 6N hydrochloric acid solution and heat by reflux, under shaking, for 15 minutes. After cooling down, the obtained solution is alkalinized by soda solution, extracted 3 times by methylene chloride. The joined organic phases are washed with a NaCl-

saturated solution, dried on Na_2SO_4 then evaporated under vacuum. The crude product (0.12g) is recrystallized in ethanol to give 0.08g of the pure compound from example 223.

Yield = 44 %

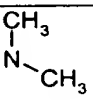
F (Tottoli) = 199°C

NMR ^1H δ (ppm) CDCl3 :

2.1 (m. 4H) ; 3.4 (m. 4H) ; 4.0 (m. 2H) ; 5.1 (d. 2H) ; 6.5-6.6 (dt. 1H) ; 6.85 (d. 1H) ; 7.0-7.3 (m. 3H) ; 7.6 (m. 1H) ; 7.7 (m. 1H) ; 8.1 (m. 1H) ; 8.45 (s. 1H) ; 8.6 (s. 1H).

The general formula (I) compounds of examples 224 to 233 in table5 are prepared by method from example 223.

TABLE 5

N° Compound	X1	R	NR4R5	Yld (%)	MP (°C)
224	7-NH2	C6H5CH2		40	240 (dec)
225	7-NH2	C6H5CH2		60	230
226	7-NH2	4-CNC6H4CH2		67	152
227	7-NH2	(E) (3-pyridyl)-CH=CHCH2		70	201
228	7-NH2	4-CNC6H4CH2		68	163
229	7-NH2	(E) C6H5CH=CHCH2		67	198
230	7-CH3NH	C6H5CH2		58	171
231	7-CH3NH	4-CNC6H4CH2		91	270
232	8-CH3NH	C6H5CH2		76	-
233	7-C2H5NH	C6H5CH2		67	225

- Compound 224 :

N.M.R.1H δ (ppm) : 1.8 – 1.9 (m. 8H) ; 3.4 – 3.45 (m. 4H) ; 4 (s. 2H) ; 5.4 (s. 2H) ; 7 (m. 1H) ; 7.25 – 7.35 (m. 3H) ; 7.55 (s. 1H) ; 7.65 – 7.80 (m. 2H) ; 8.15 – 8.2 (m. 1H)

Solvent : CDCl3

- Compound 225 :

N.M.R.1H δ (ppm) : 2.1 (m. 4H) ; 3.4 (m. 4H) ; 4 (s. 2H) ; 5.45 (s. 2H) ; 7 (d. 1H) ; 7.2 – 7.35 (m. 3H) ; 7.6 (s. 1H) ; 7.7 – 7.8 (d. 2H) ; 8 – 8.1 (d. 1H)

Solvent : CDCl3

- Compound 226 :

N.M.R.1H δ (ppm) : 2 - 2.1 (m. 4H) ; 3.35 - 3.45 (m. 4H) ; 4.05 (s. 2H) ; 8.5 (s. 2H) ; 7.05 (m. 1H) ; 7.4 – 7.5 (m. 3H) ; 7.8 (s. 1H) ; 8.05 (d. 1H)

Solvent : CDCl3

- Compound 227 :

N.M.R.1H δ (ppm) : 2.1 (m. 4H) ; 3.4 (m. 4H) ; 4 (m. 2H) ; 5.1 (d. 2H) ; 6.4 – 6.5 (dt. 1H) ; 6.9 (d. 1H) ; 7.05 (m. 1H) ; 7.2 – 7.3 (m. 2H) ; 7.35 (d. 2H) ; 7.6 (s. 1H) ; 8.1 (d. 1H)

Solvent : CDCl3

- Compound 228 :

N.M.R.1H δ (ppm) : 2.8 (s. 6H) ; 5.4 (s. 2H) ; 5.7 (m. 2H) ; 7.10 – 7.15 (m. 1H) ; 7.4 (s. 1H) ; 7.6 (d. 2H) ; 7.8 (d. 2H) ; 8.05 (d. 1H)

Solvent : DMSO

- Compound 229 :

N.M.R.1H δ (ppm) : 2.9 (s. 6H) ; 4.95 (d. 2H) ; 5.75 (m. 2H) ; 6.45 – 6.5 (dt. 1H) ; 6.7 – 6.8 (d. 1H) ; 7.2 (m. 1H) ; 7.25 – 7.4 (m. 6H) ; 8.1 (d. 1H)

Solvent : DMSO

- Compound 230 :

N.M.R.1H δ (ppm) : 2.1 (m. 4H) ; 2.95 (s. 3H) ; 3.4 (m. 4H) ; 4.1 (m. 1H) ; 5.4 (s. 2H) ; 6.95 (d. 1H) ; 7.3 (m. 3H) ; 7.45 (s. 1H) ; 7.75 (dd. 2H) ; 8.1 (d. 1H)

Solvent : CDCl3

- **Compound 231 :**

N.M.R.1H δ (ppm) : 2.1 (m. 4H) ; 2.9 (s. 3H) ; 3.4 (m. 4H) ; 5.5 (s. 2H) ; 7 (m. 1H) ; 7.45 (s. 1H) ; 7.6 (m. 2H) ; 7.8 (m. 2H) ; 8.1 (d. 1H)

Solvent : CDCl3

- **Compound 232 :**

N.M.R.1H δ (ppm) : 1.9 - 2 (m. 4H) ; 2.85 (d. 3H) ; 3.3 (m. 4H) ; 5.3 (s. 2H) ; 6.7 (d. 1H) ; 7.2 (q. 1H) ; 7.25 – 7.45 (m. 6H) ; 7.9 (d. 1H)

Solvent : DMSO

- **Compound 233 :**

N.M.R.1H δ (ppm) : 1.3 (t. 3H) ; 2.1 (m. 4H) ; 3.25 (m. 2H) ; 3.4 (m. 4H) ; 3.9 (m. 1H) ; 5.45 (s. 2H) ; 7 (m. 1H) ; 7.2 – 7.3 (m. 3H) ; 7.45 (s. 1H) ; 7.7 (m. 2H) ; 8.1 (d. 1H)

Solvent : CDCl3

Example 234 : 4-benzyl-7-(N-isopropylamino)-1-(pyrrolidin-1-yl) -4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one

In a 20 ml balloon flask, we resuspend 0.31g (0.86 mmol) of 7-amino-4-benzyl-1-(pyrrolidin-1-yl) -4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one (described in example 225) in 10 ml of methylene chloride. We add 0.14 ml (1,9 mmol) of acetone, 0.115 ml (1.9 mmol) of pure acetic acid then 0.546g (2.6 mmol) of sodium detriacetoxyborohydrid. The mixture is shaken for 48 hours at ambient temperature, under nitrogen atmosphere. The solvent is evaporated under vacuum and the residue is resuspended in ethyl acetate. The organic phase is washed in a sodium bicarbonate solution, then in NaCl-saturated solution. After drying on Na_2SO_4 and solvent elimination under vacuum, we obtain 0.3g of crude product which is purified by chromatography on silica column, after elution with mixture CH_2Cl_2 98 / CH_3OH 2 to give 0.2g of pure by CCM compound from example 234.

Yield = 58%

F(Tottoli) = 208°C [EtOH]

N.M.R.1H δ (ppm) : 1.2 (m. 6H) ; 2.05 (m. 4H) ; 3.4 (m. 4H) ; 3.7 - 3.85 (m. 2H) ; 5.5 (s. 2H) ; 6.9 (m. 1H) ; 7.2 – 7.3 (m. 3H) ; 7.4 (s. 1H) ; 7.7 (m. 2H) ; 8.1 (m. 1H)

Solvent : CDCl3

Example 235: 4-benzyl-7-methylsulfonylamino-1-(pyrrolidin-1-yl) -4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one and **example 247** : 4-benzyl-7-(N,N-dimethylsulfonylamino)-1-(pyrrolidin-1-yl) -4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

In a 20 ml balloon flask, we resuspend 0.55g (1,5 mmol) of 7-amino-4-benzyl-1-(pyrrolidin-1-yl) -4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one (described in example 225) in 10 ml of methylene chloride. We add 0.42 ml (3.0 mmol) of triethylamine then 0.24 ml (3.0 mmol) of methanesulfonyl chloride. The obtained solution is shaken for 24 hours at ambient temperature. After cooling down, the obtained solution is washed in water, dried on Na_2SO_4 then evaporated under vacuum. The crude mixture of the 2 obtained compounds (0.85g) is chromatographied on silica column by elution with the mixture CH_2Cl_2 99 / CH_3OH 1 / NH_4OH 0.1. The fractions containing the first product by elution order are joined and evaporated under vacuum to give 0.65g of 4-benzyl-7-(N,N-dimethylsulfonylamino)-1-(pyrrolidin-1-yl) -4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

F (Tottoli) = 221°C

N.M.R.1H δ (ppm) DMSO : 2.2 – 2.3 (m. 4H) ; 2.9 (s. 3H) ; 3.15 (m. 4H) ; 5.15 (s. 2H) ; 7.1 – 7.2 (m. 3H) ; 7.25 (m. 2H) ; 7.5 – 7.6 (d. 1H) ; 7.85 (s. 1H) ; 8.05 – 8.1 (d. 1H) ; 10.05 (s. 1H)

The fractions containing the second product by elution order are treated in a similar manner to give 0.15g of 4-benzyl-7-methylsulfonylamino-1-(pyrrolidin-1-yl) -4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

Yield = 23%

F(Tottoli) = 283°C [EtOH]

N.M.R.^{1}H δ (ppm) DMSO : 2 (m. 4H) ; 3.45 (m. 4H) ; 3.5 (s. 3H) ; 5.45 (s. 2H) ; 7.3 (m. 3H) ; 7.7 (m. 3H) ; 6.35 (m. 2H)

Example 236 : 7-(N,N-dimethylamino)-4-benzyl-1-(pyrrolidin-1-yl) -4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

In a balloon flask, we resuspend 0.75g (2.05 mmol) of 7-amino-4-benzyl-1-(pyrrolidin-1-yl) -4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one (described in example 225) in 0.8 ml of formic acid and 0.8 ml of formol. Under shaking, the mixture is heated at 100°C for 1 hour. After cooling down, the obtained solution is poured into iced water, the suspension is extracted

several times with ethyl acetate ; the joined organic phases are washed in a aqueous NaCl-saturated solution, dried on Na_2SO_4 then concentrated under vacuum.

The obtained crude product (0.8g) is purified by chromatography on silica column by elution with methylene mixture chloride 98 / methanol 2. We obtain 0.23g of pure by CCM product from example 236.

Yield = 29%

F (Tottoli) = 194°C [EtOH]

CCM (CH_2 Cl_2 97 / CH_3 OH 3) : Rf = 0,65

N.M.R.1H δ (ppm) : 2.1 (m. 4H) ; 3.05 (s. 6H) ; 3.45 (m. 4H) ; 5.45 (s. 2H) ; 7.1 (m. 1H) ; 7.3 (m. 3H) ; 7.6 (d. 1H) ; 7.75 (m. 2H) ; 8.1 (d. 1H)

Solvent : CDCl3

Example 237 : 4-benzyl-7-cyano-1-(N,N-dimethylamino)-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

In a 500 ml balloon flask, equipped with a shaker, refrigeration and nitrogen feeding, we add 10.8g (27,1 mmol) of 4-benzyl-7-bromo-1-(pyrrolidin-1-yl)-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one (example 164) in 100ml of N-methylpyrrolidinone (NMP). We add 4.4g (49 mmol) of cuprous cyanide then heat the mixture, under shaking and under nitrogen for 12 hours. The solvent is eliminated by evaporation under vacuum ; the residue is stirred in mixture of methylene chloride and 2N ammonia solution, the insoluble residue is eliminated by filtration, then the phases are separated by decantation. The organic phase is washed in a NaCl-saturated solution, dried on Na_2SO_4 and evaporated to give 24.0g of crude product. This is purified by chromatography on silica column by elution using mixture of ethyl acetate 65 / cyclohexane 35. The fractions pure in CCM are joined and evaporated under vacuum : we obtain 8.4g of compound from example 237.

Yield = 90%.

F (Tottoli) = 212-214°C

N.M.R.1H δ (ppm) : 2.9 (s. 6H) ; 5.3 (s. 2H) ; 7.3 (m. 3H) ; 7.5 (m. 2H) ; 8.4 (m. 1H) ; 8.5 (m. 1H) ; 8.6 (m. 1H)

Solvent : DMSO

Example 238 : 4-benzyl-7-carboxy-1-(pyrrolidin-1-yl)-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

In a 250ml balloon flask, we add 5.0 g (13,5 mmol) of 4-benzyl-7-cyano-1-(pyrrolidin-1-yl)-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one in 100ml of 16 N hydrochloric acid solution then heat by reflux for 3 hours, under shaking.

After cooling down, the precipitate is filtered, washed several times in water, dried and purified by chromatography on silica column, by elution with the mixture CH_2Cl_2 97 / CH_3OH 3, to give 2,3g of pure by CCM compound from example 238.

Yield = 44%

F(Tottoli) = 335-337°C

N.M.R.1H δ (ppm) : 1.9 (s. 4H) ; 3.4 (s. 4H) ; 5.3 (s. 2H) ; 7.3 (m. 3H) ; 7.4 (m. 2H) ; 8.2 (m. 1H) ; 8.4 (m. 1H) ; 8.7 (s. 1H)

Solvent : DMSO

Example 239 : 7-bromo-4-[(4-methoxycarbonylmethyl)benzyl]-1-(pyrrolidin-1-yl) -4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

0.8g (1,65 mmol) of 7-bromo-4-[(4-carboxymethyl)benzyl]-1-(pyrrolidin-1-yl) -4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one (example 56) and 0.25g of potassium carbonate are resuspended in 10 ml of DMF. We add 0.26g (1.82 mmol) of methyl iodide then heat at 80°C, under shaking, for 2 hours. The solvent is evaporated under vacuum, the residue is resuspended in water, this latter being extracted 3 times by ethyl acetate; the joined organic phases are washed in sodium chloride saturated solution, dried on Na_2SO_4 then the solvent is evaporated under vacuum to give 0.7g of crude product.

This is purified by chromatography on silica column by elution with mixture CH_2Cl_2 99 / CH_3OH 1. We obtain 0.5g of pure by CCM product.

Yield = 61 %

F(Tottoli) = 161-162°C [C2H5OH]

N.M.R.1H δ (ppm) : 2 - 2.1 (m. 4H) ; 3.35 – 3.45 (m. 4H) ; 3.6 (s. 2H) ; 3.7 (s. 3H) ; 5.45 (s. 2H) ; 7.2 (d. 2H) ; 7.65 (d. 2H) ; 7.85 (d. 1H) ; 8.15 (d. 1H) ; 8.5 (s. 1H)

Solvent : CDCl3

Example 240 : 7-bromo-4-[(4-(N-methylcarbamoyl)methyl)benzyl]-1-(pyrrolidin-1-yl) -4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

240-1/ 7-bromo-4-[(4-chloroformylmethyl)benzyl]-1-(pyrrolidin-1-yl) -4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

0.85g (1,76 mmol) of 7-bromo-4-[(4-carboxymethyl)benzyl]-1-(pyrrolidin-1-yl) -4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one (example XX) is added in 85 ml of dry chloroform. Under nitrogen feeding, we shake then add 0.42g (3.52 mmol) of thionyl chloride maintaining temperature below 5°C. After 90 minutes, the reaction is almost complete and chloride acid tends to precipitate as crystal. This solution will be used like in the next step.

240-2/ 7-bromo-4-[(4-(N-methylcarbamoyl)methyl)benzyl]-1-(pyrrolidin-1-yl) -4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

To the solution cooled down at 0°C of 0.6g (8.8 mmol) of methylamine chlorhydrate and 1.06g of triethylamine in 85 ml of acetone, we add slowly the obtained solution from example 240-1, maintaining temperature below 5°C. Shaking is then maintained at 0°C for 15 minutes then the obtained solution is concentrated under vacuum. We dissolve the residue in methylene chloride, wash the organic phase twice in water, dry on Na_2SO_4, evaporate the solvent under vacuum and recover then 1.0g of crude product. This is chromatographied on silica column by elution using mixture CH_2Cl_2 96 / CH_3OH 4 to give 0.4g which is recrystallized in ethanol. We obtain 0.27g of pure compound after drying.

Yield = 31 %

F (Tottoli) = 240°C

CCM (CH_2 Cl_2 92 / CH_3 OH 8) : Rf = 0.5

N.M.R.1H δ (ppm) : 1.95 - 2.1 (m. 4H) ; 2.7 (d. 3H) ; 3.35 – 3.45 (m. 4H) ; 3.5 (s. 2H) ; 5.3 – 5.5 (m. 3H) ; 7.15 (d. 2H) ; 7.65 (d. 2H) ; 7.9 (d. 1H) ; 8.2 (d. 1H) ; 8.5 (s. 1H)

Solvent : CDCl3

The compounds (I) from examples 241 to 243 (table6) are prepared according to process in example 240.

TABLE 6

N° Compound	R	NR4R5	Yld (%)	MP (°C)
241	4-(NH2COCH2)C6H4CH2		38	268
242	4-(Me2NCOCH2)C6H4CH2		74	202
243	4-(HONHCOCH2)C6H4CH2		47	229

- **Compound 241 :**

N.M.R.1H δ (ppm) : 2.7 (s. 6H) ; 3.2 (s. 2H) ; 5.1 (s. 2H) ; 6.7 (s. 1H) ; 7.05 (d. 2H) ; 7.2 (m. 3H) ; 7.95 (m. 1H) ; 8.05 (d. 1H) ; 8.15 (s. 1H)

Solvent : DMSO

- **Compound 242 :**

N.M.R.1H δ (ppm) : 2 - 2.15 (m. 4H) ; 2.9 (s. 3H) ; 2.95 (s. 3H) ; 3.35 – 3.45 (m. 4H) ; 3.7 (s. 2H) ; 5.45 (s. 2H) ; 7.15 (d. 2H) ; 7.65 (d. 2H) ; 7.85 (d. 1H) ; 8.15 (d. 1H) ; 8.5 (s. 1H)

Solvent : CDCl3

- **Compound 243 :**

N.M.R.1H δ (ppm) : 1.95 - 2.1 (m. 4H) ; 3.3 (s. 2H) ; 3.3 – 3.4 (m. 4H) ; 5.3 (s. 2H) ; 7.25 (d. 2H) ; 7.45 (d. 2H) ; 8.15 (d. 1H) ; 8.25 (d. 1H) ; 8.35 (s. 1H) ; 8.8 (s. 1H) ; 10.7 (s. 1H)

Solvent : DMSO

Example 244 : 7-methyl-4-(4-cyanobenzyl-1-(N,N-dimethylamino)-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-thione.

244-1/ 7-methyl-1-(N,N-dimethylamino)-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-thione.

In a three-necked balloon flask equipped with shaker, refrigeration and nitrogen feeding, we add 1.0g (4,1 mmol) of 7-methyl-1-(N,N-dimethylamino)-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one in 70 ml of toluene and add at once 3.3g (8.2 mmol) of Lawesson's reagent.

Under shaking, the mixture is heated by reflux for 24 hours. After cooling down, we add 30 ml of 5% hydrochloric acid solution, then we pour in 250 ml of methanol under shaking. We add 250 ml of cyclohexane and we eliminate the insoluble residue by filtration. The methanolic acid phase is separated by decantation, concentrated under vacuum and the residue is resuspended in ice and is triturated several times. The insoluble residue recovered as a resin is dissolved in 10 ml of isopropanol; from the obtained solution, shaken for 30 minutes, the yellow crystals which have precipitated are filtered, washed in isopropanol then in ether and dried under vacuum. We obtain 0.98g of product that will be used like this in the next step.

Yield = 80 %

244-2/ 4-(4-cyanobenzyl)-1-(N,N-dimethylamino)-7-methyl-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-thione.

From 0.5g (1.93 mmol) of 7-methyl-1-(N,N-dimethylamino)-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-thione (example 244-2), by using method B described in example 3, we obtain, after recrystallization in ethanol, 0.29g of compound from example 244.

Yield = 40 %

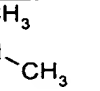
F(Tottoli) = 236°C

N.M.R.1H δ (ppm) : 2.9(s.6H) ; 3.7(s.2H) ; 5.45(s.2H) ; 7.25(m.2H) ; 7.7(m.2H) ; 7.85(m.1H) ; 8.2(d.1H) ; 8.5(s.1H)

Solvent : $CDCl_3$

The compounds (I) of examples 245 to 246 (table7) are prepared according to process in example 244.

TABLE 7

N°. Compound	X1	R	NR4R5	Yld (%)	MP (°C)
245	7-Br	4-CNC6H4CH2		13	276
246	7-CH3	(E) (pyridin-3-yl)-CH=CHCH2		26	133

- **Compound 245 :**

N.M.R.1H δ (ppm) : 2.9 (s. 6H) ; 4.7 (s. 2H) ; 7.65 (d. 2H) ; 7.75 (d. 2H) ; 8.1 (m. 2H) ; 8.4 (d. 1H)

Solvent : DMSO

- **Compound 246 :**

N.M.R.1H δ (ppm) : 2.5 (s. 3H) ; 3.0 (s. 6H) ; 4.25 (d. 2H) ; 6.45 (dt. 1H) ; 6.75 (d. 1H) ; 7.2 (m. 1H) ; 7.6 (d. 1H) ; 7.7 (d. 1H) ; 7.9 (s. 1H) ; 8.4 (m. 2H) ; 8.6 (bs. 1H)

Solvent : CDCl3

B. Intermediate compounds

Particularly preferred intermediate compounds of the current invention may be prepared according to the following examples. However, the person skilled in the art may modify easily operative procedures described below depending on the desired intermediate.

Example 250

Intermediate 1 :

1,2,3,4-tetrahydro-3-benzyl-6-bromo-4-oxo-2-thia-quinazoline from 5-bromo anthranilic acid.

In a reactor equipped with shaker, refrigeration and bromide funnel, 150 g (694 mmol) of 5-bromo-2-amino-benzoic acid are resuspended in 1.5 l of acetic acid.

Under shaking, the mixture is heated by reflux, then 92 ml (103 g ; 694 mmol) of benzyl isothiocyanate are added slowly and regularly using the bromide funnel.

After addition, shaking and heating by reflux are maintained for 6 hours, solubilization is realized gradually during this period.

After cooling down to ambient temperature, the solid that has precipitated is filtered and washed in acetic acid.

The product obtained is dried under vacuum at 60° C to give 125.2 g of expected pure by CCM compound (elution solvent: CH_2Cl_2 99.2 / CH_3OH 0.8 ; Rf = 0.9)

Yield = 52 %

NMR ^1H and ^{13}C spectra are compatible with the expected structure.

Example 251

Intermediate 2:

3, 4-Dihydro-3-benzyl-6-bromo-2-hydrazino-quinazolin-4-one.

In a reactor equipped with shaker, refrigeration, 125.2 g (360 mmol) of 1,2,3,4-tetrahydro-3-benzyl-6-bromo-4-oxo-2-thia-quinazoline (Intermediate 1) are added in 3.5 l of ethanol.

Under shaking, we add 167.6 g (3.348 mmol) of hydrazine hydrate.

The obtained suspension is heated by reflux for 18 hours, during which solubilization is gradually realized.

After cooling down to ambient temperature, about half of solvent is evaporated under vacuum and the obtained residual solution is left aside in a ice bath for 1 hour.

After filtration of the precipitate, cold ethanol wash then drying under vacuum at 60° C, we obtain 89.7 g of expected pure by CCM compound, (elution solvent: CH_2Cl_2 99 / CH_3OH 1 ; Rf = 0.1)

Yield = 72 %

NMR ^1H and ^{13}C spectra are compatible with the expected structure.

Example 252

Intermediate 3 :

4-benzyl-7-chloro-1-mercapto-4H-[1,2,4] triazolo [4, 3-a] quinazoline –5-one

In a reactor equipped with shaker and refrigeration, we resuspend 47.7 g (158 mmol) of 3,4-dihydro-3-benzyl-6-chloro-2-hydrazino-quinazolin-4-one (prepared in a similar manner as intermediate 2) in 600 ml of pyridine.

We add then 25.3 g (158 mmol) of potassium xanthogenate by fraction, the obtained solution is heated by reflux for 7 hours, under shaking, during which the solid is gradually precipitated.

After one night's rest at ambient temperature, the precipitate is separated by filtration then redissolved in 1.5 l of water.

The obtained solution is neutralized by acid acetic, then the formed precipitate is filtered, washed in water until neutral pH and dried.

We obtain 54.0 g of crude product which will be used like this in the next step.

Yield ≈ 100 %

Example 253

Intermediate 4 :

4-benzyl-7-chloro-1-méthylthio-4H-[1,2,4] triazolo [4, 3-a] quinazolin-5-one.

In a reactor equipped with a shaker and bromide funnel, we resuspend 6.72g of soda in 1200 ml of water then add 57.0 g (166 mmol) of 4-benzyl-7-chloro-1-mercapto-triazolo [4, 3-a] quinazolin-5-one (Intermediate 3).

Under shaking, we add 15.74 ml (166 mmol) of dimethyl sulfate at ambient temperature, over a 30 minutes period. Shaking is maintained for 7 hours.

After leaving aside at ambient temperature for a night, the precipitate is filtered, washed in water then dried under vacuum.

We obtain 51.2 g of crude solid which is used like this in the next step.

Yield = 100%

Example 254

Intermediate 5 : 4-benzyl-1,7-dichloro-4H-[1,2,4] triazolo [4, 3-a] quinazolin-5-one.

In a reactor equipped with shaker, plunging tube and refrigeration, we add 51.0 g (143 mmol) of 4-benzyl-7-chloro-1-methylthio-triazolo [4, 3-a] quinazolin-5-one (Intermediate 4) in a mixture of 1.5 l of chloroform and 0.9 l of water.

Under shaking, we cool down to 0° C, then allow a chlorine stream to flow, maintaining temperature below 10° C for 2 hours.

We then stop chlorine feeding, leave the mixture to return to ambient temperature then maintain shaking for 2 hours.

The 2 phases are separated by decantation, the chloroformic phase is dried on Na_2SO_4 and concentrated under vacuum .

We obtain 50.9 g of crude solid residue. This is resuspended in 400 ml of ethanol and the heterogeneous mixture is shaken for 30 minutes. The insoluble residue is filtered, washed in ethanol and dried at 50° C under vacuum to give 46.5 g of pure expected by CCM compound (elution solvent: CH_2Cl_2 99 / CH_3OH 1 ; Rf = 0.50)

Yield = 94 %

Proton and ^{13}C NMR spectra are compatible with the expected structure.

Example 255

Intermediate 6 : 4-benzyl-7-bromo-4H-[1,2,4] triazolo [4, 3-a] quinazolin-5-one.

In a 6 liter reactor, equipped with shaker, we add 89.7 g (260 mmol) of 3,4-dihydro-3-benzyl-6-bromo-2-hydrazino-quinazolin-4-one (Intermediate 2) in 2.9 l of dry chloroform.

We shake, cool the suspension down to 0° C using an ice bath, then add 216 ml (192.5 g; 1.299 mmol) of triethyl orthoformiate, leading to a slight temperature increase (up to 6° C).

Maintaining the temperature below 5° C, we add 8.2 ml of concentrated sulfuric acid in a single go. We shake then for 15 min at temperature below 5° C, then remove the ice bath, shaking is maintained for 4 additional hours during which a solid gradually precipitates.

We add 1.5 l of water and 0.7 l of chloroform, shake until complete distribution between the 2 phases then neutralize the aqueous phase to pH 7 by sodium bicarbonate.

The organic phase is decanted, washed with NaCl-saturated solution, dried on Na_2SO_4 and evaporated under vacuum to give 91.3 g of expected pure by CCM compound, (elution solvent: CH2Cl2 97 / CH3OH 3 / NH4OH 0,3 ; Rf = 0.5).

Yield = 99 %

PF (Tottoli) = 237° C

NMR ^1H and ^{13}C spectra are compatible with the expected structure.

Example 256

Intermediate 7 :

4-benzyl-1, 7-dibromo-4H-[1,2,4] triazolo [4, 3-a] quinazolin-5-one.

In a 3 liter reactor equipped with shaker, refrigeration and bromide funnel, we add 35 g (98.5 mmol) of 4-benzyl-7-bromo-4H-[1,2,4] triazolo [4,3-a]quinazoline-5-one (Intermediate 6) in 630 ml of chloroform and 11 ml of pyridine.

Under shaking, 16.4 ml (320 mmol) of bromine are then added at ambient temperature over a 30 minute period.

After addition, shaking is maintained at ambient temperature for 1 hour ; the reaction medium is then distributed between 1 l of water and 1.5 l of chloroform and the heterogeneous mixture shaken for 15 min.

The insoluble residue is dried, washed in water to a neutral pH then triturated in ethanol.

After drying under vacuum at 50 ° C, we obtain a first fraction of 8.2 g of pure by CCM expected compound (elution solvent : CH_2Cl_2 99 / CH_3OH 1 ; Rf = 0.6).

After separation of the chloroformic phase, washing in sodium bicarbonate solution then in water, drying on Na_2SO_4, evaporation of solvent under vacuum then triturating of residue in ethanol, filtration and drying of solid at 50° C, we obtain 33.1 g of a second fraction of expected compound, equivalent by CCM to the precedent fraction.

Yield total (of the 2 fractions) = 96%

NMR ^1H spectrum is compatible with the expected structure.

Example 257

Intermediate 8 : 1-Azepanyl-4H-[1,2,4] triazolo[4,3-a] quinazolin-5-one

In a 150 ml balloon flask equipped with shaker and refrigeration , we dissolve 1.0 g (2.68 mmol) of 1-Azepanyl-4-benzyl-4H-[1,2,4] triazolo[4,3-a] quinazolin-5-one in 60 ml of tetrahydrofuran.

We add 2.0 g of ammonium formiate then 1.5 g of 10 % activated palladium on charcoal.

The mixture is shaken and heated by solvent reflux for 5 hours.

After cooling down, the suspension is filtered, and then the solvent is evaporated under vacuum to give 0.55 g of residual solid.

This is chromatographied on silica column by elution using mixture $CH_2 Cl_2$ 97 / $CH_3 OH$ 3 ; the fractions pure in CCM are gathered together and concentrated under vacuum to give 0,42 g of residual solid.

Yield = 55%

F (Tottoli) = 222 – 224°C

CCM ($CH_2 Cl_2$ 95 / $CH_3 OH$ 5) : Rf = 0,4

N.M.R.^1H δ (ppm) : 1.65-1.85 (m. 8H) ; 3.25 (m. 4H) ; 7.5 (t.1H) ; 7.9 (t. 1H) ; 8.15 (d. 1H) ; 8.3 (d.1H) ; 12.6 (m. 1H)

Solvent : DMSO

The compounds (I ; R = H) of examples 258 to 262 (table8) are prepared according to the process in example 257.

TABLE 8

N° Compound	X1	NR4R5	Yld (%)	MP (°C)
258	7-Br		96	>290
259	8-CH3		64	-
260	8- 		75	-
261	7-Br		89	>300
262	7-Br		90,5	>300

Example 263

Intermediate 9 : 1-Azepanyl-7-chloro-4H-[1,2,4] triazolo[4,3-a] quinazolin-5-one

10.0 g of 1-Azepanyl-4-benzyl-7-chloro-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (24,5mmol) then 19.6 g (147 mmol) of dry aluminium chloride are resuspended in 200 ml of anhydrous benzene.

The suspension is shaken and heated at 50° C in the absence of humidity.

After 90 minutes, we allow to cool down, add some ice to the reaction mixture then shake the mixture vigorously for 30 minutes.

The obtained precipitate is dried, washed in water to a neutral pH and dried at 50°C to give 7.5 g of pure by CCM solid.

Yield = 96 %

F (Tottoli) : >300°C

CCM ($CH_2 Cl_2$ 95 / CH_3 OH 5) : Rf = 0.35

N.M.R.^{1}H δ (ppm) : 1.65-1.9 (m. 8H) ; 3.3 (m. 4H) ; 7.95 (d. 1H) ; 8.05 (s. 1H) ; 8.3 (d. 1H) ; 12.8 (m.1H)

TABLE 9

N° Compound	X1	NR4R5	MP (°C)
264	H		283
265	7-CH3		298
266	7-CH3		>300
267	7-CH3		-
268	7-OH		295
269	7-CN		>300
270	7-CN		-

Example 271

Intermediate 10 : 1-amino-4-benzyl-7-bromo-4H-[1,2,4] triazolo[4,3-a] quinazolin-5-one

In a 500ml reactor equipped with shaker, refrigeration equipped with a potash keeper, thermometer and nitrogen feeding, we resuspend 5.0g (14.5 mmol) of 3, 4-dihydro-3-benzyl-6-bromo-2-hydrazino-quinazolin-4-one (prepared according example XX) in 150 ml of dry methanol. We add 1.62g (15.3 mmol) of cyanogene bromide and shake the heterogeneous mixture for 1 hour at ambient temperature, then by reflux for 5 hours After cooling down, we add drop by drop, under vigorous shaking, aqueous solution of saturated sodium bicarbonate to pH 8. The insoluble solid is filtered, washed several times in water and dried under vacuum to give 4.9g of crude product.

The latter is triturated in 100 ml of methanol, the insoluble fraction is separated by filtration, washed in methanol and dried under vacuum. We obtain 4.6g of pure by CCM product. NMR ^{1}H and ^{13}C spectra are compatible with the expected structure.

Yield = 86.5 %

F (Tottoli) = 287°C

CCM ($CH_2 Cl_2$ 95 / $CH_3 OH$ 5) : Rf = 0.5

Evaluation of *in vitro* activity of the preferred compounds of the invention

Inhibition of the phosphodiesterase

The capacity of the formula (I) compounds of the invention to inhibit the cyclic nucleotide phosphodiesterases is evaluated by their CI_{50} measurement (necessary concentration to inhibit 50 % of enzymatic activity).

The type 4 phosphodiesterases are obtained from a cytosolic preparation extracted from the human origin cellular line U937 according to a method adapted from T.J. Torphy and al., 1992, J.Pharm.Exp. Ther. 263 : 1195-1205

The other classes of phosphodiesterases are obtained after partial purification FPLC on Mono Q column. (anion exchange column) according to a method adapted from **Lavan B. E., Lakey T., Houslay M. D.** Biochemical Pharmacology, 1989, 38(22), 4123-4136., and from **Silver P.J and** al., 1988, Eur.J. Pharmacol. 150 : 85-94, either, from human origin cellular lines for PDE 1 (monocytar line TPH1) and PDE5 (line MCF7 issued from an adenocarcinoma), or from dog aorta for PDE 3, or for the human PDE3A, from gene cloning in insect cells SF21 in baculovirus, according to a method adapted from Luckow, V. A. and al., 1991 in Recombinant DNA Technology&Applications.,eds. Prokop, Bajpai,R.K.&Ho,C.S., pp97-152.

The enzymatic activity measurement of the different PDE classes, and in particular the PDE 4, is performed according to a method adapted from W.J. Thompson and al. 1979, Advances in Cyclic Nucleotide Research, Vol. 10 : 69-92, ed. G. Brooker and al. Raven Press, NY.

For the CI_{50} determination, the enzymatic activity is measured in the presence of inhibitor within concentration margins of 0.1 to 100µM.

The following table illustrates the PDE4 inhibitory activity from enzymatic preparation obtained from the line U937.

N° Compound	IC_{50} (μM)	N° compound	IC_{50} (μM)	N° compound	IC_{50} (μM)
1	0.054	59	0.090	190	0.19
3	0.079	60	0.050	218	0.048
11	0.080	61	0.011	223	0.012
13	0.060	62	0.053	224	0.075
20	0.04	75	0.078	227	0.028
22	0.41	76	0.070	229	0.080
32	0.053	78	0.038	230	0.002
34	0.056	79	0.14	231	0.00027
35	0.020	80	0.073	233	0.18
37	0.015	81	0.016	234	2.69
40	0.014	83	0.012	239	0.005
41	0.018	85	0.041	240	0.013
42	0.024	89	0.027	242	0.011
43	0.030	92	0.030	243	0.028
44	0.090	94	0.029	246	0.041
46	0.090	96	0.058		
47	0.050	98	0.029		
48	0.025	102	0.060		
49	0.080	103	0.039		
50	0.035	104	0.077		
51	0.027	164	0.090		
52	0.030	186	0.090		
57	0.014	189	0.078		

The examination of the results from the above table shows that the preferred products of the invention tested in the trial inhibit the enzyme PDE4 in vitro in an efficient manner.

Inhibition of TNFα production by human leukocytes stimulated by lipopolysaccharid

This test aims to evaluate capacity of the compounds of the invention to inhibit TNFα (tumor necrosis-α) production by human leukocytes in the presence of high human serum concentration (75%). Indeed, it appears that a number of compounds having a capacity any longer to inhibit phosphodiesterase 4 in enzymatic or cellular tests do not present anymore this capacity when the test is performed in human blood. The test described here is based on the use of human leukocytes cultivated in 75% of human serum. It had been previously documented that these conditions simulate the observed situation when TNFα dosage is performed in human blood.

The compounds to test are dissolved into 20 mM (sometimes 6 mM) of DMSO. 100 µl of DMSO are distributed into 7 wells of a a 96 well microtiter plate (wells B to H). 150 µl of the compound solution are distributed into line A wells. 50 µl are then sequentially transferred 7 times. 20 µl of this serial dilutions of compounds are sequentially transferred twice in wells containing 180 µl of RPMI 1640 (Gibco). 50 µl of these dilutions are then transferred in wells where cells will be added.

Each test includes a series of eight wells without LPS (100% of inhibition), eight wells with LPS (0% of inhibition) and a series of Rolipram dilutions in order to enable comparison of the tests between each other and then to evaluate their variability.

A leukocyte vial is unfrozen in bain-marie (37°C), its content is transferred into a 15 ml tube containing 10 ml of RPMI added with 5% of human serum (RPMI-5% HS). The cells are sedimented (800 g, 6 minutes, 4°C), resuspended in 10 ml of the same medium and counted by dilution in Trypan blue solution. After centrifugating (800 g, 6 minutes, 4°C), the cells are resuspended to 2 x 10^6/ml in human serum.

To 50 µl aliquots of different dilutions of compounds, 100 µl of cells are added. The plates are then incubated 30 minutes at 37°C, then 50 µl of solution 4 µg/ml of LPS prepared in human serum are added. The plates are incubated for the night at 37°C.

After incubation for 15-18 hours, 90 µl of growth supernatant are taken and transferred into rounded-bottom microtiter wells. The TNFα presence is then evaluated by ELISA (Pharmingen) by using 50 µl of supernatant. The protocol described by the manufacturer is strictly applied.

Results obtained for some of the preferred compounds of the current invention are illustrated in the following table.

Compound	Inhibition (human leukocytes) IC_{50} μM
3	3.4
104	8.1
94	6.3
101	8.6
85	6.8
98	-
79	5.2
91	-
93	4.3
103	10.7
46	-
35	-

Evaluation of *in vivo* activity f compounds of the invention

***In vivo* TNFα model in Wistar rat**

The TNFα is a cytokin playing a central role in inflammation mechanisms. Its production may be induced by injection of lipopolysaccharid (LPS). It has been shown that the intracellular AMPc increase, produced in particular by PDE4 inhibitors, decreases the TNFα production in *in vitro* and *in vivo* models. Therefore it matters here to quantify *in vivo* anti-inflammatory potential of the compounds of the invention, administrated by oral route (p.o.) by measuring inhibition of TNFα production in plasma in rat, the latter having received a intraperitoneal injection (i.p.) of lipopolysaccharid (LPS). The treatment by the compounds of the invention or the carrier is administrated by oral route in male Wistar rats, 30 min. before LPS injection. The rats are sacrificed 90 min. after LPS stimulation, the blood is harvested on EDTA and TNFα concentration is measured in each plasma sample. The results obtained from some of the compounds of the current invention are presented in the table below.

Compound	% Inhibition to 10 mg/kg
3	- 98 %
104	- 94 %
94	- 87 %
101	- 80 %
85	- 77 %
98	- 75 %
79	- 72 %
91	- 70 %
93	- 67 %
103	- 64 %
46	- 58 %
35	- 51 %

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Model of eosinophily in rat

The studies undertaken from this experimental model aim to evaluate inhibitory effect of the compounds of the invention on the rush of inflammatory cells and in particular of eosinophils in the opening of trachea-bronchial shaft in rat. The eosinophils play a major role in asthma physiopathology in human by releasing on the level of pulmonary parenchyma some pro-inflammatory mediators like leukotriens, proteins and specific enzymes (ECP, EPO, MBP) and cytokins. The massive recruitment of this cellular type air passages in asthmatic patient leads to a progressive degradation of pulmonary tissue explaining bronchial hyperactivity, chronic disease and exacerbation in the absence of treatment. This model uses Brown Norway rats, whose particularity is to produce, like atopic patients, immunoglobulin E (IgE) rates in response to a sensibilization by antigen. The protocol used involves two sensibilizations to ovalbumin at fourteen days interval then a challenge seven days later with ovalbumin aerosol. Forty-eight hours after the antigenic challenge, the animals undergo a bronchoalveolar wash under anesthesia in order to harvest inflammatory cells infiltrate in lung. These cells are then counted and differentiated according to morphological criteria. The products of the invention are administrated by oral route, 1 hour before the antigenic challenge. Most of the preferred compounds of the current invention tested in this model have also demonstrated an excellent activity.

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Model of neutrophily in mouse

The studies undertaken from this experimental protocol aim to evaluate modulating effect of the compounds of the invention on the rush of pro-inflammatory cells (precocious phase) in the opening of trachea-bronchial shaft in mouse. This cellular rush is consecutive to stimulation simulating a bacterial infection (bacterial lipopolysaccharid or LPS). This precocious inflammatory step results from events combination among which the main ones are synthesis and release of stimulating (TNFαi) and chimiotactic (IL-8ii) factors, increase of vascular permeability at trachea-bronchial micro-circulation level and neutrophilic polynuclear infiltration which is concomitant to plasmatic protein exudation in pulmonary tissues.

This pathological process is retrieved in chronic obstructive broncho-pneumopathy disease (COPD) in which neutrophils, with macrophage, play a key role in launching of neutrophil recruitment amplification, but also in destructuration of pulmonary tissues (decline of pulmonary functions), hypersecretion of trachea-bronchial mucus (clogging of aerial tracts), tissular inflammation (release of inflammatory mediators and free radicals) and basal tonus increase of pulmonary muscular smooth fibers (chronic respiratory distress). Some of the compounds of the examples have demonstrated an activity in this model.

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